JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

5-Substituted-2-furaldehydes: A Synthetic Protocol Utilizing an Organozinc Route

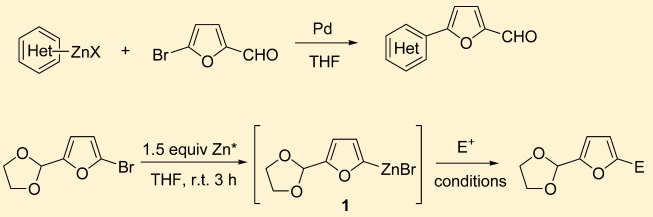
Seung-Hoi Kim[†] and Reuben D. Rieke*[,‡]

[†]Department of Chemistry, Dankook University, 29 Anseo, Cheonan 330-714, Korea

[‡]Rieke Metals, Inc., 1001 Kingbird Rd., Lincoln, Nebraska 68521, United States

Supporting Information

ABSTRACT: Facile synthetic routes for the preparation of a wide range of 5-substituted 2-furaldehydes have been revealed. They were accomplished through either Pd-catalyzed cross-coupling reaction of various aryl- and heteroarylzinc halides with 5-bromo-2-furaldehyde or utilization of a new organozinc reagent, 5-(1,3-dioxolan-2-yl)-2-furanylzinc bromide, which was easily prepared by the direct insertion of highly active zinc to 2-(5-bromofuran-2-yl-1,3-dioxolane. Of special note is the uniqueness of using a new organozinc reagent, representing a first example of the direct synthesis of the corresponding organozinc halide. The subsequent coupling reactions in various types of reaction conditions led to the formation of somewhat different furan derivatives. It is also of significance that all of the cross-coupling reactions were carried out under mild conditions.



INTRODUCTION

Widespread applications of furan-containing derivatives can be found in a wide range of chemical industries such as pharmaceuticals, textiles, dyes, fossil fuels, photo sensitizers, cosmetics, and even in agrochemicals.[1] This rich variety of applicability is attributed to the preparation of numerous furan derivatives. In general, the preparation methods for these derivatives consist of two approaches, ring construction and derivatization of preformed furan rings. Among these, the latter case is a more readily accessible route since many of these derivatives are commercially available.

It is significant that the furan moiety is an interesting structural unit playing a prominent role especially in natural products that show a wide range of biological activity.[2] Of special interest are aryl-substituted furan intermediates, which have been intensively used in the preparation of furan-containing pharmaceuticals.[2a] Due to the particular interest in this area, considerable time and effort has been spent in the development of a versatile synthetic methodology for the preparation of 2,5-disubstituted furan derivatives.

Among the better-known procedures as depicted in Scheme 1, transition-metal-catalyzed cross-coupling reactions of the corresponding organometallic reagents are one of the predominant approaches.[3] Of these organometallics, unfortunately, little work has been performed using arylmetallic reagents. O'Doherty described the preparation of 5-aryl-2-furaldehydes using palladium-catalyzed cross-coupling reaction of protected furylstannes and/or furylzincs (routes **A** and **B**, Scheme 1).[4] Recently, a similar approach using a one-pot, four-step sequence palladium-catalyzed cross-coupling reaction of triorganozincates was reported by Gauthier et al. (route **B**, Scheme 1).[5] The organometallic reagents used in these studies were prepared by the lithiation of the protected furans followed by transmetalation. Generally, cryogenic conditions are required for the lithiation of organic compounds. McClure et al. has reported a one-pot synthesis of 5-aryl-2-furaldehydes via the Suzuki coupling reaction prepared using protected furan moiety route **B**, Scheme 1) and also the regioselective palladium-catalyzed direct arylation of 2-furaldehyde (route **C**, Scheme 1).[6] More recently, simple 2-substituted furan derivatives were prepared by iron- and palladium-catalyzed coupling reaction using the Grignard and Suzuki coupling reagents.[7] Knochel has also reported the regio- and chemoselective synthesis of highly substituted furans using Grignard reagents.[8]

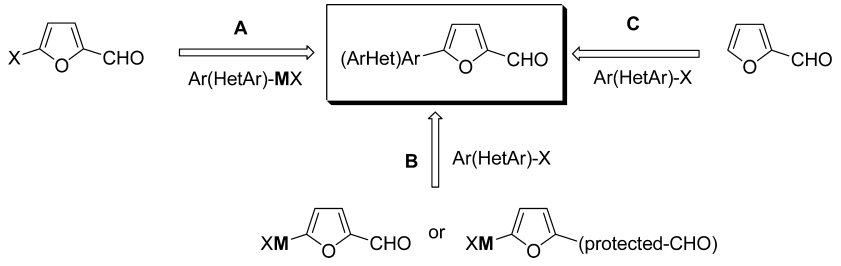
Despite the present methodologies, there is still a need to introduce a convenient route for the preparation of a variety of 5-substituted furaldehydes. Thus, we herein would like to report an alternative synthetic route providing a unique way of preparing highly functionalized 2-furaldehydes under mild conditions.

To explore the variety of ways of the preparation of furan derivatives, our attention was focused on the utilization of organozinc reagents that were readily accessible. It is well-known that the use of organozinc reagents is advantageous over the other organometallics such as the Grignard, Suzuki, and Stille coupling reactions mainly because of the functional group tolerance of the organozincs. The arylzinc reagents used in the coupling reactions with 5-bromo-2-furaldehyde[9] in this study (Tables 1, 2, and 3) were easily prepared by the direct insertion of highly active zinc (Rieke zinc) to the corresponding aryl

Special Issue: Howard Zimmerman Memorial Issue

Received: September 18, 2012
Published: October 17, 2012

Scheme 1. Representative Synthetic Routes for 5-Substituted 2-Furaldehydes



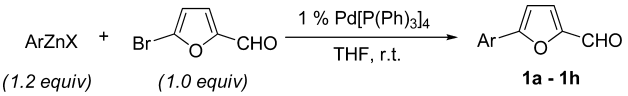
halides.[10] It was also of interest that all of the subsequent cross-coupling reactions of the resulting organozincs were efficiently carried out in the presence of a catalytic amount of Pd(0)-catalyst under very mild conditions affording the cross-coupling products in good to excellent yield. A wide range of 5-substituted 2-furaldehydes were provided through this methodology, and the results are summarized in Tables 1, 2, and 3.

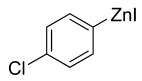
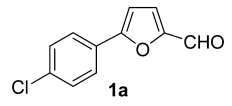
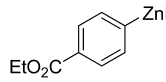
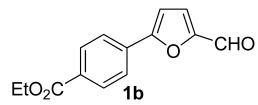
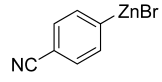
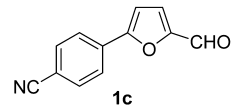
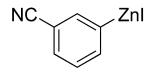
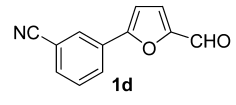
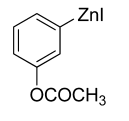
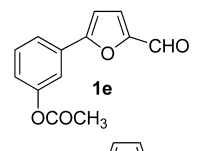
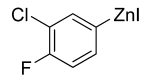
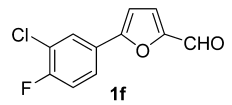
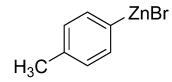
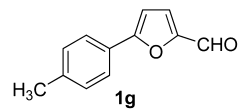
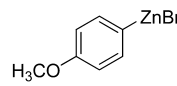
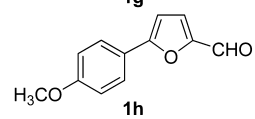
RESULTS AND DISCUSSION

Our first attempt was conducted with arylzinc halides bearing various functionalities. As described in Table 1, many functionalized arylzinc halides underwent the coupling reaction with 5-bromo-2-furaldehyde under the mild conditions (1 mol % $Pd[P(Ph)_3]_4$, room temperature) and successfully gave 5-aryl-substituted 2-furaldehydes. In the case of electron-withdrawing groups (Table 1, entries 1–4), excellent yields (82–93%) were achieved with the exception of 3-cyanophenylzinc iodide (42%, **1d**, entry 4, Table 1). For most of the cases, the reactions were completed in 1 h at room temperature. However, when 4-methylphenylzinc bromide bearing an electron-donating group was treated with 5-bromo-2-furaldehyde under the same conditions (room temperature, 1 h) used above (Table 1, entry 7), the corresponding cross-coupling product (**1g**, Table 1) was obtained in slightly reduced yields (55%). GC–MS analysis showed that the major impurity was the unreacted 5-bromo-2-furaldehyde. Thus, in the following coupling reaction containing another electron-donating group, 4-methoxyphenylzinc bromide, a longer reaction time was employed to lead the coupling reaction to completion yielding **1h** (Table 1, entry 8). With this coupling product (**1h**), a more interesting result was observed. The color of the isolated product was immediately changed from light yellow to greenish black upon storage at atmosphere. Presumably, we assumed that this was caused by air-oxidation, but no further study of this observation was executed.

In addition to the results above, the Pd(0)-catalyzed coupling reaction is also applicable to the synthesis of several different types of 5-heteroaryl-2-furaldehydes. Again, the aforementioned mild reaction conditions worked well for the following coupling reactions. The results are summarized in Table 2. Expansion of this strategy was first conducted by the coupling reaction of thienylzinc bromides containing a halogen atom, 1,3-dioxane, and ester functionalities. As described in entries 1–3 in Table 2, the corresponding products (**2a**, **2b**, and **2c**, respectively) were obtained in good to excellent isolated yields. Significantly, these functionalities derived from the corresponding organozinc reagents could be used for the further modification along with the aldehyde at the 2-position of the furan ring. Unfortunately, product **2b** appears to be an unstable compound, which leads to the formation of self-deprotected mixture upon storage at room temperature. It is of interest that

Table 1. Coupling Reactions with Arylzinc Halides



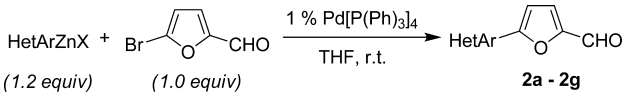
Entry	Arylzinc	Time(h)	Product	Yield(%)[a]
1		1.0	 **1a**	93
2		0.5	 **1b**	82
3		1.0	 **1c**	91
4		0.5	 **1d**	42
5		0.5	 **1e**	92
6		1.0	 **1f**	90
7		1.0	 **1g**	55
8		24	 **1h**	(96)[b]

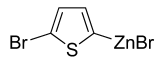
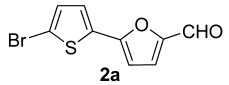
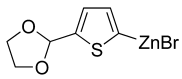
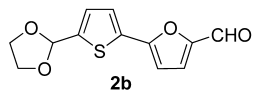
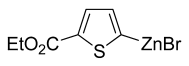
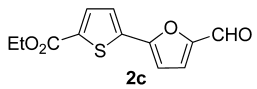
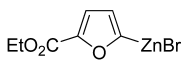
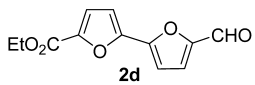
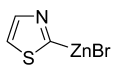
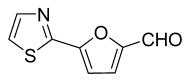
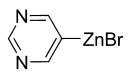
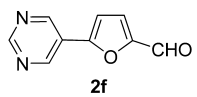
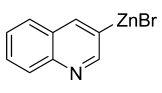
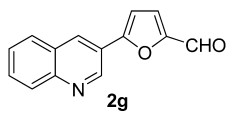
[a]Isolated yield (based on furaldehyde). [b]Conversion by GC, no isolated product.

an unsymmetrical furan–furan linkage (**2d**, Table 2) has been constructed in 83% isolated yield by treatment with 5-ethoxycarbonyl-2-furylzinc bromide (Table 2, entry 4). We also examined the use of heteroarylzinc bromides possessing two hetero atoms in a ring compound such as 2-thiazoylzinc and 5-pyrimidylzinc bromides. As noted in entries 5 and 6 in Table 2, yields (43% and 33%) were somewhat lower than other heteroarylzincs. 3-Quinolinylzinc bromide appeared to be a good coupling partner for 5-bromo-2-furaldehyde resulting in the formation of **2g** in moderate yield (Table 2, entry 7).

dx.doi.org/10.1021/jo301836x | J. Org. Chem. 2013, 78, 1984–1993

Table 2. Coupling Reactions with Heteroarylzinc Halides

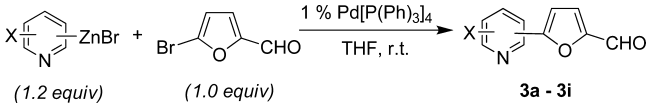


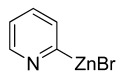
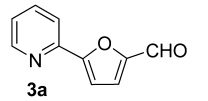
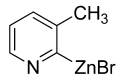
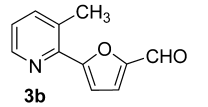
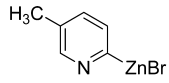
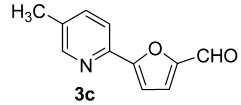
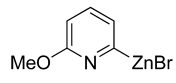
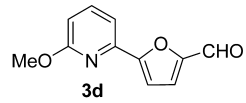
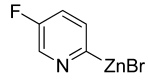
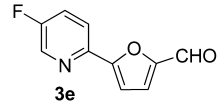
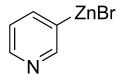
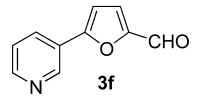
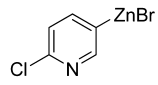
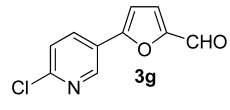
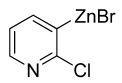
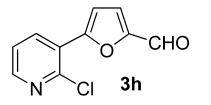
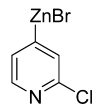
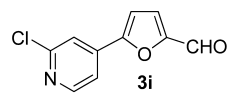
Entry	Organozinc	Time(h)	Product	Yield(%)[a]
1		1.0	 **2a**	75
2		0.5	 **2b**	95
3		0.5	 **2c**	92
4		1.0	 **2d**	83
5		24	 **2e**	43
6		24	 **2f**	33
7		24	 **2g**	41

[a]Isolated yield (based on furaldehyde).

To magnify the scope of our methodology, special heteroarylzinc reagents, pyridylzinc halides was chosen and employed in the coupling reaction with 5-bromo-2-furaldehyde since 5-pyridyl-2-furaldehydes have been frequently used for synthetic intermediates in pharmaceuticals.[5] The pyridylzinc halides used in this study were also easily prepared by the direct oxidative addition of active zinc to the corresponding halides.[11] As summarized in Table 3, the coupling reactions were carried out under the same reaction conditions as used in the previous study (a catalytic amount of $Pd[P(Ph_3)]_4$ at room temperature in THF). An excellent yield was obtained from the reaction of simple 2-pyridylzinc bromide in 1 h (Table 3, entry 1). Sterically hindered organozinc, 3-methyl-2-pyridylzinc bromide, required a prolonged reaction time affording **3b** in lower yield (Table 3, entry 2). The coupling reaction of 5-methyl-2-pyridylzinc bromide, however, was completed in 6 h at room temperature to produce **3C** in good yield (Table 3, entry 3). An extended time (24 h) was required for the methoxy-substituted pyridylzinc bromide at room temperature in THF (Table 3, entry 4). 2-Pyridylzinc bromide containing a fluorine atom was successfully employed in the coupling reaction with 5-bromo-2-furaldehyde to give the coupled product **3e** in 60% yield (Table 3, entry 5). Along with the 2-pyridylzinc reagents, 3-pyridylzinc bromides (Table 3, entries 6−8) were also easily reacted with 5-bromo-2-furaldehyde at room temperature in THF to afford the corresponding products (**3f**, **3g**, and **3h**, Table 3) in good to excellent yields. Moreover, in the reaction with 2-chloro-4-pyridylzinc bromide, the coupling reaction proceeded smoothly to give **3i** in 66% yield (Table 3, entry 9).

Table 3. Pd-Catalyzed Coupling Reactions with Pyridylzincs



Entry	RZnX	Time(h)	Product	Yield(%)[a]
1		1	 **3a**	92
2		24	 **3b**	56
3		6	 **3c**	80
4		24	 **3d**	50
5		6	 **3e**	60
6		6	 **3f**	85
7		1	 **3g**	95
8		6	 **3h**	72
9		6	 **3i**	66

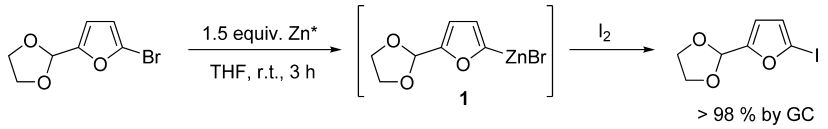
[a]Isolated yield (based on furaldehyde).

Even though those approaches used above provided a variety of furan derivatives, we developed a somewhat different approache for the preparation of 5-substituted 2-furalhehydes containing a unique functionality on 5-position. One of the reasons is that some of the organozinc reagents bearing especially hydroxy- and amino- functionalities are not readily available using the direct insertion method. More interestingly, introducing a carbonyl group on 5-position is not obtainable from the methodology used in previous approaches. In contrast to this fact, it is successfully accomplished by the direct preparation of furylzinc reagent and its subsequent application for the coupling reaction in our study (route **B** in Scheme 1).

As shown in Scheme 2, 5-(1,3-dioxolan-2-yl)-2-furanylzinc bromide **1** was easily prepared as expected by the direct insertion of active zinc to 2-(5-bromofuran-2-yl)-1,3-dioxolane under mild conditions. To confirm the formation of the corresponding organozinc reagent, an aliquot of the reaction mixture was quenched with iodine and analyzed by GC and GC−MS. Both analyses clearly showed the formation of 2-(5-iodofuran-2-yl)-1,3-dioxolane. From this result, it could be inferred that the corresponding organozinc reagent (**1**) was

dx.doi.org/10.1021/jo301836x | J. Org. Chem. 2013, 78, 1984−1993

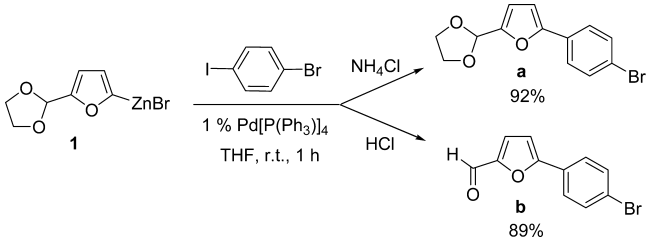
Scheme 2. Preparation of 5-(1,3-Dioxolan-2-yl)-2-furanylzinc Bromide (1)



successfully formed. To find out the usefulness of the resulting organozinc reagent, subsequent coupling reactions were performed with a variety of different types of electrophiles such as aromatic halides, haloamines, haloalcohols, and carboxylic acid chlorides.

Prior to the general applications of 5-(1,3-dioxolan-2-yl)-2-furanylzinc bromide **1**, a typical Pd-catalyzed C−C bond-forming reaction with 1-bromo-4-iodobenzene was carried out. As described in Scheme 3, two derivatives were achieved depending upon the workup procedure.

Scheme 3. Preparation of 5-Aryl-substituted Furans



The coupling reaction was completed in 1 h at room temperature in THF in the presence of 1 mol % $Pd[P(Ph_3)]_4$. As is typical, an acidic workup procedure gave rise to the 5-(4-bromophenyl)-2-furaldehyde (**b**) in 89% isolated yield. Meanwhile, a protected furaldehyde (**a**) was obtained from the workup procedure using ammonium chloride in excellent yield.

As described in the aforementioned report,[5] these types of molecules are easily accessible via the cross-coupling reaction of 2-bromo-5-furaldehyde with the corresponding organozinc regents. In order to produce more complex molecules, we have tried several new reaction conditions. Table 4 shows the results observed from Pd-catalyzed cross-coupling reactions with a variety of aryl bromides. In an effort to evaluate the overall feasibility of the organozinc **1**, coupling reactions with 2-bromo-5-furaldehyde were carried out first to obtain a pseudosymmetrical bifuraldehyde under the conditions depicted in Table 4.

The reaction proceeded smoothly at room temperature and was completed in 30 min. Even though the formation of the cross-coupling product was confirmed by GC and GC−MS, unfortunately, the separation of coupling product failed due to the instability of the product in the atmosphere (entry 1, Table 4). However, the similar compound **4b** that has an ester functionality was successfully produced in 63% isolated yield (entry 2, Table 4). The next attempt was to couple some aromatic bromides for which the corresponding organozinc reagents were not readily available from the direct insertion method using active zinc route.[12] Use of the $Pd(OAc)_2$/SPhos catalytic system successfully afforded the coupling product **4c** in 73% isolated yield (entry 3, Table 4). In the following several reactions (entries 4−7 in Table 4), it should be emphasized that no extra ligand was necessary for the coupling reaction in the presence of $Pd[P(Ph_3)]_2Cl_2$. It worked effectively in the coupling reaction at room temperature with tetramethylphenyl, *tert*-butylphenyl, and acenaphthyl bromides leading to the corresponding products, **4d**, **4e**, and **4f** in excellent yields (entries 4−6, Table 4), respectively. This condition was also very effective with an electron-rich *N*,*N*-dimethylaminophenyl bromide (entry 7, Table 4).

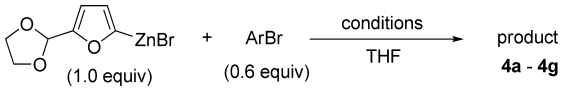
We then attempted the coupling reaction with haloaromatic compounds containing a hydroxyl or an amino functional group that would be more challenging. Even though there are very limited examples of coupling reactions of organozinc compounds with haloaromatic alcohols and amines,[11] to our best knowledge no report revealed the coupling reaction with furanylzinc bromide. In our study, the coupling reaction was easily accomplished using 2 mol % $Pd(OAc)_2$ and 4 mol % SPhos in THF at room temperature. As described in Table 5, it was found that some of the coupling products were not stable enough to be obtained as an isolated product in the atmosphere. It was of interest that the stability of the coupling product is dependent upon the position of the functional group of the aromatic ring. For instance, 4-iodophenol was coupled well with **1** under mild conditions affording the corresponding product, **5a**, in 92% isolated yield (entry 1, Table 5). In contrast, even though the formation of the expected coupling products (**5b** and **5c**) was confirmed by GS−MS analysis of the reaction aliquot from the reaction using 3-iodophenol and 2-iodophenol, respectively, the isolated products (**5b** and **5c**) immediately decomposed upon solvent removal after column chromatography (entries 2 and 3, Table 5). In the case of employing aniline, a similar result was also observed. Again, we were not able to isolate the coupling product **5d** using 4-iodoaniline (entry 5, Table 5). Meanwhile, 3-iodoaniline was coupled with **1** giving rise to a stable coupling product **5e** in 80% isolated yield as an orange oily product (entry 6, Table 5). Regarding the stability of the products described above, again no further investigations were performed.

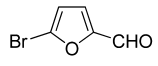
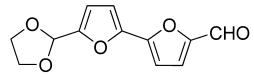
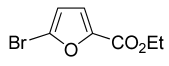
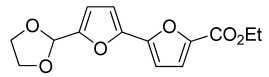
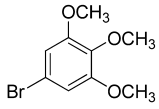
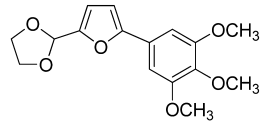
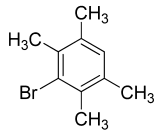
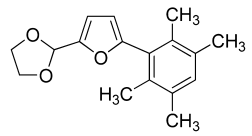
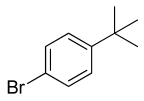
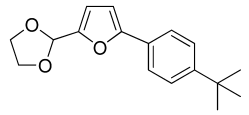
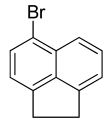
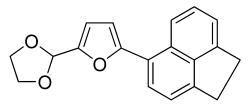
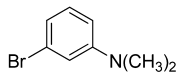
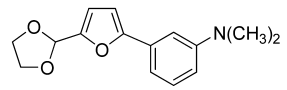
Subsequent investigation of this chemistry was focused on introducing a carbonyl group in the 5-position of furan. To this end, copper-catalyzed coupling reactions with an acid chloride were applied since this methodology has been one of the most widely used strategies in Negishi coupling. The first attempt was carried out with benzoyl chloride in a standard fashion (10 mol % CuI and 20 mol % LiCl). The coupling product **6a** was achieved in excellent isolated yield (93%, entry 1, Table 6). Alkyl acid chlorides (entries 3 and 4, Table 6) were also coupled with **1** to generate ketones **6c** and **6d** in good yields. It should be mentioned that the heterocyclic acid chlorides were also successfully employed in the coupling reaction with **1**, providing unsymmetrical heterocyclic ketones **6e** and **6f** in moderate to good yields (entries 5 and 6, Table 6), respectively. An interesting result was that trifluoroacetic anhydride was also a good coupling partner, and the coupling reaction with **1** gave ketone **6g** in moderate yield (entry 7, Table 6). Finally, a S_N2'-type reaction was performed with allyl bromide resulting in the formation of 2-(5-allylfuran-2-yl)-1,3-dioxolane **6h** in 70% yield (entry 8, Table 6).

In conclusion, facile synthetic routes for the preparation of a wide range of 5-substituted 2-furaldehydes have been revealed.

dx.doi.org/10.1021/jo301836x | J. Org. Chem. 2013, 78, 1984−1993

Table 4. Pd-Catalyzed Synthesis of 2-(5-Aryfuran-2-yl)-1,3-dioxolanes



Entry	Halide	Conditions	Product	Yield(%)[a]
1		1 % $Pd(PPh_3)_4$ r.t. 30 min		**4a** (98%)[b]
2		1 % $Pd(PPh_3)_4$ r.t. 24 h		**4b** 63
3		2 % $Pd(OAc)_2$ 4 % SPhos r.t. overnight		**4c** 73
4		5 % $Pd(PPh_3)_2Cl_2$ r.t. 24 h		**4d** 64
5		5 % $Pd(PPh_3)_2Cl_2$ r.t. 2 h		**4e** 82
6		5 % $Pd(PPh_3)_2Cl_2$ r.t. 2 h		**4f** 93
7		5 % $Pd(PPh_3)_2Cl_2$ r.t. 5 h		**4g** 92

[a]Isolated yield (based on aryl halide), otherwise mentioned. [b]Conversion by GC, no isolated product.

They were accomplished through either Pd-catalyzed cross-coupling reaction of various aryl- and heteroarylzinc halides with 5-bromo-2-furaldehyde (route **A**) or utilization of a new organozinc reagent, 5-(1,3-dioxolan-2-yl)-2-furanylzinc bromide **1**, which was easily prepared by the direct insertion of highly active zinc to 2-(5-bromofuran-2-yl-1,3-dioxolane (route **B**). Of special note is the uniqueness of the route **B**, representing a first example of the direct synthesis of the corresponding organozinc halide. The subsequent coupling reactions of **1** in various types of reaction conditions led to the formation of somewhat different furan derivatives, such as a furan possessing a hydroxy or aminophenyl substituent and a furan bearing a carbonyl group directly attached at the 5-position. It is also of significance that all of the cross-coupling reactions were carried out under mild conditions.

EXPERIMENTAL SECTION

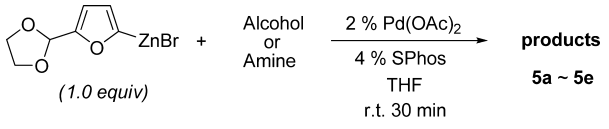
All reactions were carried out under positive argon pressure. Active zinc was prepared by a literature method.[10] Other commercially available reagents including the solvent (THF, from Sigma-Aldrich) were used without further purification. Flash chromatography was performed on Kieselgel 60 (230−400 mesh). NMR spectra were recorded at 300 or 500 MHz using $CDCl_3$ (TMS) as a solvent. Chemical shifts (δ) are reported in part per million (ppm) for ^1H and ^{13}C NMR spectra. The coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra (HRMS-TOF) are measured with electron impact (EI). All melting points are uncorrected.

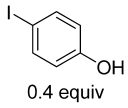
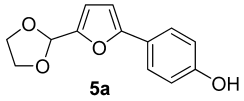
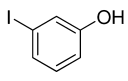
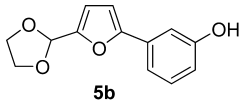
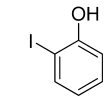
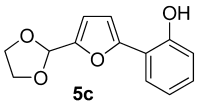
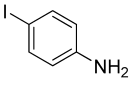
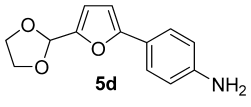
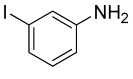
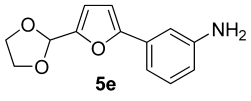
General Procedure for Pd-Catalyzed Cross-Coupling Reactions. *5-(4-Chlorophenyl)furan-2-carbaldehyde* ***1a.*** A 50 mL round-bottomed flask equipped with a stirring bar, a thermometer, and a septum was charged with 0. 1g of $Pd[P(Ph)_3]_4$, and then 20 mL of a 0.5 M solution of 4-chlorophenylzinc bromide (10 mmol) in THF was added into the flask via a syringe. Next, 1.40 g (8 mmol) of 5-bromofuran-2-carbaldehyde was cannulated while being stirred at room temperature. After 1.0 h of stirring at room temperature, the reaction mixture was quenched with saturated 3 M HCl solution and then extracted with ether, which was washed with saturated $Na_2S_2O_3$ and brine and then dried over $MgSO_4$. The mixture was purified by a flash column chromatography on a silica gel column (10% EtOAc/90% heptane) to afford 0.77 g of **1a** as a white solid in 93% isolated yield: mp 127−128 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.68 (s, 1 H), 7.77 (d, J = 10.0 Hz, 2 H), 7.44 (d, J = 10.0 Hz, 2 H), 7.33 (d, J = 5.0 Hz, 1 H), 6.85 (d, J = 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.2, 158.2, 152.1, 135.7, 129.3, 127.5, 126.5, 116.8, 108.0; HRMS (EI) for $[C_{11}H_7O_2Cl]$ calcd 206.0135, found 206.0142; GC−MS (EI, 70 eV) m/z (%) 206 (100) $[M^+]$, 178 (10), 151 (20), 149 (59), 115 (22).

5-(4-Ethoxycarbonylphenyl)furan-2-carbaldehyde ***1b.*** Following the general procedure, 0.80 g of **1b** was obtained as a salmon solid in 82% isolated yield: mp 122−123 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.70 (s, 1H), 8.12 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 3.5 Hz, 1H), 6.96 (d, J = 3.5 Hz, 1H), 4.41 (q, J = 7.0 Hz, 2H),

dx.doi.org/10.1021/jo301836x | J. Org. Chem. 2013, 78, 1984−1993

Table 5. Coupling with Haloamines and Alcohols



Entry	Halide	Product	Yield(%)[a]
1	 0.4 equiv	 **5a**	92
2	 0.4 equiv	 **5b**	(>98%)[b]
3	 0.4 equiv	 **5c**	(>98%)[b]
4	 0.8 equiv	 **5d**	(>98%)[b]
5	 0.8 equiv	 **5e**	80

[a]Isolated (based on halide), otherwise mentioned. [b]Conversion by GC, no isolated product.

1.42 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 165.9, 157.9, 152.5, 132.7, 131.1, 130.2, 125.0, 109.4, 61.3, 14.3.

4-(5-Formylfuran-2-yl)benzonitrile ***1c***. Following the general procedure, 0.72 g of **1c** was obtained as a pale orange solid in 91% isolated yield: mp 163 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 3.5 Hz, 1H), 7.01 (d, J = 3.5 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 156.7, 152.8, 132.8, 125.6, 122.9, 118.4, 112.8, 110.1; GC–MS (EI, 70 eV) m/z (%) 197 (100) [M^+], 169 (8), 140 (60), 113 (16).

3-(5-Formylfuran-2-yl)benzonitrile ***1d***. Following the general procedure, 0.33g of **1d** was obtained as a beige solid in 42% isolated yield: mp 195–196 °C (dec.); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.73 (s, 1H), 8.11 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.37 (d, J = 3.5 Hz, 1H), 6.96 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 156.44, 152.6, 132.6, 130.3, 130.0, 129.1, 128.6, 123.0, 118.1, 113.5, 109.1.

3-(5-Formylfuran-2-yl)phenyl Acetate ***1e***. Following the general procedure, 0.0.76 g of **1e** was obtained as a yellow oil in 83% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.66 (s, 1H), 7.67 (d, J = 5.0 Hz, 1H), 7.58 (s, 1H), 7.46 (t, J = 5.0 Hz, 1H), 7.31 (d, J = 5.0 Hz, 1H), 7.15–7.13 (m, 1H), 6.86–6.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.4, 169.4, 158.2, 152.1, 151.2, 130.1, 129.9, 122.9, 122.7, 120.3, 117.0, 108.4, 65.9, 21.1; HRMS (EI) for [$C_{13}H_{10}O_4$] calcd 230.0579, found 230.0578; GC–MS (EI, 70 eV) m/z (%) 230 (26) [M^+], 188 (100), 160 (15), 131 (30), 102 (11), 77 (18).

5-(3-Chloro-4-fluorophenyl)furan-2-carbaldehyde ***1f***. Following the general procedure, 0.81g of **1f** was obtained as a beige solid in 90% isolated yield: mp 106–107 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.66 (s, 1H), 7.88 (d, J = 3.0 Hz, 1H), 7.86 (d, J = 3.0 Hz, 1H), 7.71–7.66 (m, 1H), 7.32 (d, J = 6.0 Hz, 1H), 7.22 (t, J = 9.0 Hz, 1H), 6.81 (d, J = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.4, 160.6, 157.2, 152.5, 127.8, 126.5, 125.4, 123.5, 122.4, 117.6, 108.3; HRMS (EI) for [$C_{11}H_6O_2ClF$] calcd 224.0040, found 224.0042.

5-(4-Methylphenyl)furan-2-carbaldehyde ***1g***. Following the general procedure, 0.41g of **1g** was obtained as a yellow solid in 55% isolated yield: mp 57–58 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.65 (s, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 3.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 3.5 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.1, 159.8, 151.8, 140.1, 129.7, 126.3, 125.3, 123.9, 107.1, 21.5; GC–MS (EI, 70 eV) m/z (%) 186 (100) [M^+], 158 (10), 129 (63), 115 (9), 77 (8).

5-(4-Methoxyphenyl)furan-2-carbaldehyde ***1h***. Following the general procedure, 0.56 g of **1h** was obtained as pale yellow oil. However, the product was immediately oxidized to an unidentified product upon the expose to the air after column chromatography. The structure was confirmed by GC–MS (EI, 70 eV) m/z (%) 202 (100) [M^+], 187 (50), 174 (10), 159 (25), 145 (38).

5-(5-Bromothiophen-2-yl)furan-2-carbaldehyde ***2a***. A 50 mL round-bottomed flask equipped with a stirring bar, a thermometer, and a septum was charged with 0.1 g of Pd[$P(Ph)_3$]$_4$, and then 20 mL of 0.5 M solution of 5-bromo-2-thienylzinc bromide (10 mmol) in THF was added into the flask via a syringe. Next, 1.40 g (8 mmol) of 5-bromofuran-2-carbaldehyde was cannulated while being stirred at room temperature. After 1.0 h of stirring at room temperature, the reaction mixture was quenched with saturated 3 M HCl solution and then extracted with ether, which was washed with saturated $Na_2S_2O_3$ and brine and then dried over $MgSO_4$. The mixture was purified by a flash column chromatography on a silica gel column (10% EtOAc/90% heptane) to afford 1.54 g of **2a** as a pale yellow solid in 75% isolated yield: mp 91–92 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.64 (s, 1H), 7.29 (d, J = 3.5 Hz, 1H), 7.28 (d, J = 4.0 Hz, 1H), 7.08 (d, J = 4.0 Hz, 1H), 6.65 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.9, 153.5, 151.6, 133.1, 131.1, 126.3, 115.0, 107.7; HRMS (EI) for [$C_9H_5O_2BrS$] calcd 257.9173, found 257.9178.

5-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)furan-2-carbaldehyde ***2b***. Following the general procedure, 0.95 g of **2b** was obtained as a yellow oil in 95% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.63 (s, 1H), 7.42 (d, J = 5.0 Hz, 1H), 7.29 (d, J = 5.0 Hz, 1H), 7.16 (d, J = 5.0 Hz, 1H), 6.68 (d, J = 5.0 Hz, 1H), 6.13 (s, 1H), 4.14–4.09 (m, 2H), 4.05–4.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.4, 154.5, 152.5, 144.3, 132.2, 126.7, 125.8, 107.8, 99.9, 65.3; GC–MS (EI, 70 eV) m/z (%) 250 (57) [M^+], 221 (13), 205 (40), 191 (41), 178 (100), 150 (13), 121 (32).

Ethyl 5-(5-Formylfuran-2-yl)thiophene-2-carboxylate ***2c***. Following the general procedure, 0.92 g of **2c** was obtained as a salmon solid in 92% isolated yield: mp 84–85 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.69 (s, 1H), 7.77 (d, J = 4.0 Hz, 1H), 7.48 (d, J = 4.0 Hz, 1H), 7.32 (d, J = 3.5 Hz, 1H), 6.81 (d, J = 3.5 Hz, 1H), 4.39 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.2, 161.7, 153.4, 152.1, 137.3, 134.9, 133.9, 126.0, 109.3, 61.6, 14.3

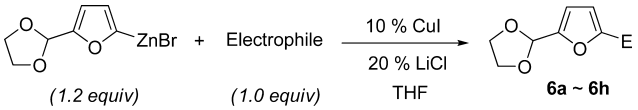
Ethyl 5-(5-Formylfuran-2-yl)furan-2-carboxylate ***2d***. Following the general procedure, 0.78 g of **2d** was obtained as a yellow solid in 83% isolated yield: mp 81–82 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.66 (s, 1H), 7.32 (d, J = 3.5 Hz, 1H), 7.24 (d, J = 3.5 Hz, 1H), 6.96 (d, J = 3.5 Hz, 1H), 6.94 (d, J = 3.5 Hz, 1H), 4.38 (q, J = 7.0 Hz, 2H), 1.38 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.3, 158.3, 152.3, 149.7, 147.6, 145.3, 122.9, 119.4, 110.5, 109.9, 61.3, 14.3; HRMS (EI) for [$C_{12}H_{10}O_5$] calcd 234.0528, found 234.0532.

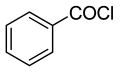
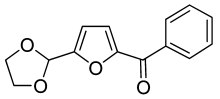
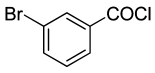
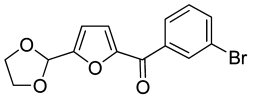
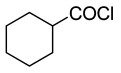
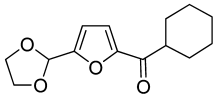
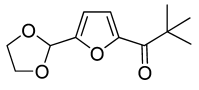
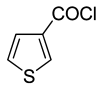
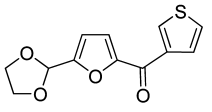
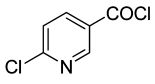
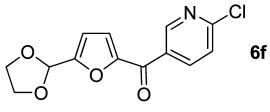
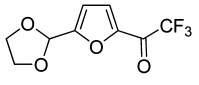
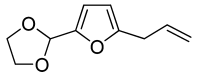
5-(Thiazol-2-yl)furan-2-carbaldehyde ***2e***. Following the general procedure, 0.31g of **2e** was obtained as a pale yellow solid in 43% isolated yield: mp 70–71 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 7.94 (d, J = 3.0 Hz, 1H), 7.49 (d, J = 3.0 Hz, 1H), 7.36 (d, J = 3.5 Hz, 1H), 7.18 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.6, 156.4, 153.2, 152.2, 144.5, 128.5, 122.4, 120.7, 110.5; HRMS (EI) for [$C_8H_5NO_2S$] calcd 179.0041, found 179.0047.

5-(Pyrimidin-5-yl)furan-2-carbaldehyde ***2f***. Following the general procedure, 0.23 g of **2f** was obtained as an off-white solid in 33% isolated yield: mp 164–165 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.77 (s, 1H), 9.25 (s, 1H), 9.18 (s, 2H), 7.39 (d, J = 3.5 Hz, 1H), 7.05 (d, J = 3.5 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 158.7, 153.2, 153.1, 153.0, 123.7, 110.0; HRMS (EI) for [$C_9H_6N_2O_2$] calcd 174.0429, found 174.0434.

dx.doi.org/10.1021/jo301836x | J. Org. Chem. 2013, 78, 1984–1993

Table 6. Cu-Catalyzed Coupling Reaction



Entry	Electrophile	Condition	Product	Yield(%)[a]
1		0 °C ~ r.t. /1 h	 **6a**	93
2		0 °C ~ r.t. /1 h	 **6b**	83
3		0 °C ~ r.t. /1 h	 **6c**	90
4		0 °C/1 h	 **6d**	89
5		0 °C ~ r.t. /1 h	 **6e**	75
6		r.t. 1 h	 **6f**	83
7	$(CF_3CO)_2O$	0 °C/1 h	 **6g**	65
8		r.t. 1 h	 **6h**	70

[a]Isolated yield (based on electrophile).

5-(Quinolin-3-yl)furan-2-carbaldehyde ***2g***. Following the general procedure, 0.37 g of **2g** was obtained as a beige solid in 41% isolated yield: mp 150 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 9.30 (s, 1H), 8.64 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 3.5 Hz, 1H), 7.08 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.3, 156.7, 152.6, 148.1, 147.1, 131.9, 130.6, 129.5, 128.4, 127.7, 127.5, 123.6, 122.3, 108.9, 103.8.

5-(Pyridin-2-yl)furan-2-carbaldehyde ***3a***. Into a 50 mL round-bottomed flask equipped with a stirring bar, a thermometer, and a septum were added $Pd(PPh_3)_4$ (0.10 g, 1 mol %) and 5-bromo-2-furaldehyde (1.40g, 8.0 mmol) under an argon atmosphere. Next, 20 mL of 2-pyridylzinc bromide (0.5 M in THF, 10.0 mmol) was added via a syringe. The resulting mixture was stirred at room temperature for 1.0 h, quenched with saturated NH_4Cl solution, and then extracted with ethyl acetate (10 mL × 3), which was washed with saturated $Na_2S_2O_3$ solution and brine and then dried over anhydrous $MgSO_4$. Purification by column chromatography on silica gel (20% ethyl acetate/80% heptane) afforded 5-(2-pyridyl)-2-furaldehyde (**3a**, 1.28 g) as a white solid in 92% isolated yield: mp 87–88 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.70 (s, 1 H), 8.63 (d, J = 5.0 Hz, 1 H), 7.90 (d, J = 5.0 Hz, 1 H), 7.77, (dt, J = 5.0 Hz, 1 H), 7.34 (d, J = 5.0 Hz, 1 H), 7.28 (m, 1 H), 7.26 (d, J = 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.7, 158.3, 152.6, 150.0, 147.8, 137.0, 136.9, 124.0, 120.1, 110.7; HRMS (EI) for $[C_{10}H_7NO_2]$ calcd 173.0477, found 173.0477; GC–MS (EI, 70 eV) m/z (%) 173 (100) [M$^+$], 144 (25), 116 (36), 89 (32), 63 (20).

5-(3-Methylpyridin-2-yl)furan-2-carbaldehyde ***3b***. Following the general procedure, 0.85 g of **3b** was obtained as a creamy solid in 56% isolated yield: mp 113–114 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 8.53 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.38–7.37 (m, 1H), 7.2–7.20 (m, 2H), 2.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.8, 159.5, 152.6, 147.3, 146.4, 139.8, 131.7, 123.6, 121.9, 112.9, 20.5.

5-(5-Methylpyridin-2-yl)furan-2-carbaldehyde ***3c***. Following the general procedure, 0.60 g of **3c** was obtained as a beige solid in 80% isolated yield: mp 100 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.67 (s, 1H), 8.45 (s, 1H), 7.58–7.56 (m, 1H), 7.33 (d, J = 3.5 Hz, 1H), 7.17 (d, J = 3.5 Hz, 1H), 2.54 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.6, 158.7, 152.3, 150.5, 145.3, 137.3, 133.9, 123.3, 119.8, 110.0, 18.5; GC–MS (EI, 70 eV) m/z (%) 187 (100) [M$^+$], 158 (34), 130 (42), 103 (12), 77 (24).

5-(6-Methoxypyridin-2-yl)furan-2-carbaldehyde ***3d***. Following the general procedure, 0.41 g of **3d** was obtained as a pale brown solid in 50% isolated yield: mp 93–94 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.70 (s, 1H), 7.69–7.65 (m, 1H), 7.55–7.53 (m, 1H), 7.35 (d, J = 3.5 Hz, 1H), 7.21 (d, J = 3.5 Hz, 1H), 6.77 (d, J = 1.0 Hz, H),

dx.doi.org/10.1021/jo301836x | J. Org. Chem. 2013, 78, 1984–1993

4.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.6, 163.9, 158.6, 152.4, 145.1, 139.2, 123.2, 113.0, 111.8, 110.6, 53.4.

5-(5-Fluoropyridin-2-yl)furan-2-carbaldehyde ***3e***. Following the general procedure, 0.46 g of **3e** was obtained as an off-white solid in 60% isolated yield: mp 107−108 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.72 (s, 1H), 8.52 (d, J = 2.5 Hz, 1H), 7.97−7.95 (m, 1H), 7.5−7.51 (m, 1H), 7.36 (d, J = 3.5 Hz, 1H), 7.20 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.6, 160.3, 158.2, 157.5, 152.5, 144.2, 138.5, 123.6, 123.3, 121.3, 110.5; HRMS (EI) for $[C_{10}H_6NO_2F]$ calcd 191.0383, found 191.0389.

5-(Pyridin-3-yl)furan-2-carbaldehyde ***3f***. Following the general procedure, 1.18 g of **3f** was obtained as an off-white solid in 85% isolated yield: mp 100−101 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.72 (s, 1H), 9.06 (s, 1H), 8.64−8.63 (m, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.42−7.40 (m, 1H), 7.36 (d, J = 3.5 Hz, 1H), 6.96 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.4, 156.3, 152.6, 150.3, 146.7, 132.2, 125.2, 123.8, 123.1, 108.8; GC−MS (EI, 70 eV) m/z (%) 173 (100) [M^+], 145 (7), 116 (51), 89 (26), 63 (32).

5-(6-Chloropyridin-3-yl)furan-2-carbaldehyde ***3g***. Following the general procedure, 0.79 g of **3g** was obtained as a beige solid in 95% isolated yield: mp 169−170 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.72 (s, 1H), 8.84 (s, 1H), 8.10 (dd, J = 2.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 3.5 Hz, 1H), 6.96 (d, J = 3.5 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.4, 155.1, 152.8, 152.1, 146.4, 134.9, 124.7, 124.3, 123.0, 109.2; GC−MS (EI, 70 eV) m/z (%) 207 (100) [M^+], 179 (9), 150 (47), 115 (15), 63 (18).

5-(2-Chloropyridin-3-yl)furan-2-carbaldehyde ***3h***. Following the general procedure, 0.61 g of **3h** was obtained as a white solid in 72% isolated yield: mp 103−104 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 8.45−8.43 (m, 1H), 8.39 (dd, J = 2.0 Hz, 1H), 7.47 (d, J = 4.0 Hz, 1H), 7.43−7.41 (m, 1H), 7.40 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 153.1, 152.3, 149.3, 147.7, 137.3, 124.9, 122.8, 114.2.

5-(2-Chloropyridin-4-yl)furan-2-carbaldehyde ***3i***. Following the general procedure, 0.55 g of **3i** was obtained as an off-white solid in 66% isolated yield: mp 115−116 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.77 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 7.73 (s, 1H), 7.60 (d, J = 5.5 Hz, 1H), 7.37 (d, J = 3.5 Hz, 1H), 7.10 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.7, 154.5, 153.1, 152.7, 150.5, 138.6, 122.2, 119.4, 117.6, 111.5; GC−MS (EI, 70 eV) m/z (%) 207 (100) [M^+], 179 (5), 150 (31), 115 (10), 89 (17), 63 (19).

Preparation of 5-(1,3-Dioxolan-2-yl)-2-furanylzinc Bromide. In an oven-dried 50 mL round-bottomed flask equipped with a stir bar was added 0.93 g of active zinc (Zn*, 14.25 mmol). 2-(5-Bromofuran-2-yl)-1,3-dioxolane (2.08 g, 9.5 mmol) was then cannulated neat into the flask at room temperature. The resulting mixture was stirred at room temperature for 3 h. The whole mixture was allowed to settle, and then the supernatant was used for the subsequent coupling reactions.

Ethyl 5-(5-(1,3-Dioxolan-2-yl)furan-2-yl)furan-2-carboxylate ***4b***. In a 25 mL round-bottomed flask was added $Pd[P(Ph_3)]_4$ (0.06 g, 1 mol %) under an argon atmosphere, and then 10 mL of 5-(1,3-dioxolan-2-yl)-2-furanylzinc bromide (0.5 M in THF, 5.0 mmol) was added via a syringe. Next, ethyl 5-bromofuran-2-carboxylate (0.88 g, 4.0 mmol) was added into the flask. The resulting mixture was stirred at room temperature overnight, quenched with saturated NH_4Cl solution, and then extracted with ethyl ether (10 mL × 3). Washed with saturated $Na_2S_2O_3$ solution and brine, then dried over anhydrous $MgSO_4$. Purification by column chromatography on silica gel (10% ethyl acetate/90% heptane) afforded ethyl 5-(5-(1,3-dioxolan-2-yl)furan-2-yl)furan-2-carboxylate (**4b**, 0.70 g) in 63% isolated yield as a light yellow viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21 (d, J = 5.0 Hz, 1 H), 6.77 (d, J = 5.0 Hz, 1 H), 6.67 (d, J = 5.0 Hz, 1 H), 6.53 (d, J = 5.0 Hz, 1 H), 5.97 (s, 1 H), 4.37 (q, J = 5.0 Hz, 2 H), 4.13 (m, 2 H), 4.04 (m, 2 H), 1.38 (t, J = 5.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.8, 152.0, 149.4, 145.9, 143.9, 119.7, 110.7, 108.6, 107.4, 97.7, 65.4, 61.1, 14.5; GC−MS (EI, 70 eV) m/z (%) 259 (100) [M^+], 214 (20), 200 (53), 187 (30).

5-(5-(1,3-Dioxolan-2-yl)furan-2-yl)furan-2-carbaldehyde ***4a***. The formation of the desired product was confirmed by GC−MS (EI, 70 eV) m/z (%) 234 (767) [M^+], 205 (23), 189 (25), 175 (68), 162 (100), 133 (31), 105 (22).

2-(5-(3,4,5-Trimethoxyphenyl)furan-2-yl)-1,3-dioxolane ***4c***. Following the general procedure, 0.67 g of **4c** was obtained as a yellow solid in 73% isolated yield: mp 104−105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.89 (s, 2H), 6.53 (q, J = 3.0 Hz, 2H), 6.00 (s, 1H), 4.15 (m, 2H), 4.05 (m, 2H), 3.91 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.6, 153.7, 150.7, 138.2, 126.4, 110.7, 105.3, 101.7, 98.1, 65.3, 61.1, 56.4; HRMS (EI) for $[C_{16}H_{18}O_6]$ calcd 306.1103, found 306.1108.

2-(5-(2,3,5,6-Tetramethylphenyl)furan-2-yl)-1,3-dioxolane ***4d***. Following the general procedure, 0.52 g of **4d** was obtained as a white solid in 64% isolated yield: mp 117−118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (s, 1H), 6.54 (d, J = 3.0 Hz, 1H), 6.19 (d, J = 3.0 Hz, 1H), 5.96 (s, 1H), 4.16−4.12 (m, 2H), 4.02−3.98 (m, 2H), 2.23 (s, 6H), 2.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.2, 150.4, 134.9, 133.8, 132.4, 131.2, 109.8, 109.5, 98.2, 65.3, 20.2, 17.1; HRMS (EI) for $[C_{17}H_{20}O_3]$ calcd 272.1412, found 272.1410.

2-(5-(4-tert-Butylphenyl)furan-2-yl)-1,3-dioxolane ***4e***. Following the general procedure, 0.67 g of **4e** was obtained as a light orange oil in 82% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, J = 10 Hz, 2H), 7.39 (d, J = 10 Hz, 2H), 6.55 (d, J = 5.0 Hz, 1H), 6.50 (d, J = 5.0 Hz, 1H), 5.99 (s, 1H), 4.17−4.13 (m, 2H), 4.0−4.01 (m, 2H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.9, 150.9, 150.5, 128.0, 125.7, 124.0, 110.6, 105.0, 98.1, 65.3, 34.8, 31.4; GC−MS (EI, 70 eV) m/z (%) 272 (100) [M^+], 257 (100), 227 (16), 213 (55), 185 (63), 157 (16), 115 (17), 73 (22).

2-(5-(1,2-Dihydroacenaphthylen-6-yl)furan-2-yl)-1,3-dioxolane ***4f***. Following the general procedure, 0.82 g of **4f** was obtained as a light brown oil in 93% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 (d, J = 10 Hz, 1H), 7.75 (d, J = 10 Hz, 1H), 7.50−7.47 (m, 1H), 7.30−7.27 (m, 2H), 6.68 (d, J = 5.0 Hz, 1H), 6.59 (d, J = 5.0 Hz, 1H), 6.05 (s, 1H), 4.20−4.15 (m, 2H), 4.05−4.00 (m, 2H), 3.39−3.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.6, 150.6, 146.9, 146.5, 139.8, 128.8, 128.4, 127.3, 123.8, 121.0, 119.8, 119.2, 110.5, 108.3, 98.2, 65.4, 30.6, 30.3; GC−MS (EI, 70 eV) m/z (%) 292 (100) [M^+], 248 (15), 233 (70), 220 (45), 189 (25), 152 (16).

3-(5-(1,3-Dioxolan-2-yl)furan-2-yl)-N,N-dimethylbenzenamine ***4g***. Following the general procedure, 0.71 g of **4g** was obtained as a yellow oil in 92% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24−7.06(m, 3H), 6.69(br s, 1H), 6.59(d, J = 5.0 Hz, 1H), 6.50 (d, J = 5.0 Hz, 1H),6.01 (s, 1H), 4.18−4.14 (m, 2H), 4.06−4.03 (m, 2H), 3.02 (s,6H); GC−MS (EI, 70 eV) m/z (%) 259 (100) [M^+], 228 (5), 214 (19), 200 (54), 187 (30).

4-(5-(1,3-Dioxolan-2-yl)furan-2-yl)phenol ***5a***. In a 25 mL round-bottomed flask, $Pd(OAc)_2$ (0.02 g, 2.0 mol %), SPhos (0.08 g, 4.0 mol %) and THF (5 mL) were placed. Next, 5-(1,3-dioxolan-2-yl)-2-furanylzinc bromide (0.5 M in THF, 10 mL) was added slowly. After being stirred for 1 h at room temperature, quenched with saturated NH_4Cl solution, then extracted with ethyl acetate (10 mL × 3), which was washed with saturated $Na_2S_2O_3$ solution and brine and then dried over anhydrous $MgSO_4$. Purification by column chromatography on silica gel (20% ethyl acetate/80% heptane) afforded 4-(5-(1,3-Dioxolan-2-yl)furan-2-yl)phenol (**5a**, 0.85 g) as a beige solid in 92% isolated yield; mp 150−152 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (d, J = 10.0 Hz, 2 H), 6.83 (d, J = 10.0 Hz, 2 H), 6.50 (d, J = 5.0 Hz, 1 H), 6.45 (d, J = 5.0 Hz, 1 H), 5.99 (s, 1 H), 5.20 (br s, 1 H), 4.18 (t, J = 5.0 Hz, 2 H), 4.05 (t, J = 5.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.5, 154.9, 149.9, 125.9, 115.77, 110.9, 104.0, 98.1, 65.6; GC−MS (EI, 70 eV) m/z (%) 232 (100) [M^+], 187 (22), 173 (100), 160 (58), 131 (42), 73 (41).

3-(5-(1,3-Dioxolan-2-yl)furan-2-yl)phenol ***5b***. Following the general procedure; the formation of the desired product was confirmed by GC−MS (EI, 70 eV) m/z (%) 232 (100) [M^+], 187 (43), 173 (99), 160 (86), 131 (57), 73 (80).

2-(5-(1,3-Dioxolan-2-yl)furan-2-yl)phenol ***5c***. The conversion to the corresponding product was confirmed by GC.

4-(5-(1,3-Dioxolan-2-yl)furan-2-yl)benzenamine ***5d***. The formation of the desired product was confirmed by GC−MS (EI, 70 eV) m/z (%) 231 (100) [M^+], 200 (6), 187 (14), 172 (95), 159 (34), 130 (33).

dx.doi.org/10.1021/jo301836x | J. Org. Chem. 2013, 78, 1984−1993

3-(5-(1,3-Dioxolan-2-yl)furan-2-yl)benzenamine ***5e***. Following the general procedure, 0.74 g of **5e** was obtained as light brown oil in 80% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15 (t, J = 5.0 Hz, 1H), 7.06 (d, J = 5.0 Hz, 1H), 7.01 (br s, 1H), 6.60−6.58 (m, 1H), 6.55 (d, J = 5.0 Hz, 1H), 6.49 (d, J = 5.0 Hz, 1H), 6.00 (s, 1H), 4.19−4.16 (m, 2H), 4.06−4.04 (m, 2H), 3.48 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.9, 150.6, 146.8, 131.6, 129.7, 114.8, 114.7, 110.7, 105.6, 98.1, 65.4; GC−MS (EI, 70 eV) m/z (%) 231 (100) [M^+], 186 (29), 172 (79), 159 (93), 130 (40).

5-(1,3-Dioxolan-2-yl)furan-2-yl-(phenyl)methanone ***6a***. Following the general procedure, 0.91 g of **6a** was obtained as a colorless oil in 93% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (s, 1H), 7.95 (d, J = 5.0 Hz, 1H), 7.58 (t, J = 10 Hz, 1H), 7.49 (t, J = 10 Hz, 2H), 7.19(d, J = 5.0 Hz, 1H), 6.91 (d, J = 5.0 Hz, 1H), 6.04 (s, 1H), 4.16−4.13 (m, 2H), 4.09−4.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 182.6, 156.4, 152.4, 137.3, 132.8, 129.5, 128.6, 120.9, 110.4, 97.6, 65.5.

5-(1,3-Dioxolan-2-yl)furan-2-yl-(3-bromophenyl)methanone ***6b***. Following the general procedure, 1.07 g of **6b** was obtained as a viscous yellow oil in 83% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (s, 1H), 7.90 (d, J = 5.0 Hz, 1H), 7.71 (d, J = 5.0 Hz, 1H), 7.38 (t, J = 5.0 Hz, 1H), 7.22 (d, J = 5.0 Hz, 1H), 6.63 (d, J = 5.0 Hz, 1H), 6.03 (s, 1H), 4.19−4.13 (m, 2H), 4.10−3.74 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.8, 156.9, 152.0, 138.9, 135.7, 132.5, 130.2, 128.1, 122.8, 121.3, 110.1, 97.5, 65.6; GC−MS (EI, 70 eV) m/z (%) 323 (12) [M^+], 279 (10), 183 (15), 155 (12), 139 (100), 95 (24).

5-(1,3-Dioxolan-2-yl)furan-2-yl-(cyclohexyl)methanone ***6c***. In a 25 mL round-bottomed flask, CuI (0.10 g, 10 mol %) and LiCl (0.04 g, 20 mol %) and HF (5 mL) were placed and then the flask was cooled down to 0 °C using an ice-bath. 5-(1,3-Dioxolan-2-yl)-2-furanylzinc bromide (0.5 M in THF, 10 mL) was added. Cyclohexanecarbonyl chloride (0.59 g, 4.0 mmol) was slowly added while being stirred at 0 °C. After being stirred for 1 h, quenched with saturated NH_4Cl solution, then extracted with ethyl acetate (10 mL × 3). Washed with saturated $Na_2S_2O_3$ solution and brine, then dried over anhydrous $MgSO_4$. Purification by column chromatography on silica gel (20% ethyl acetate/80% heptane) afforded 5-(1,3-dioxolan-2-yl)furan-2-yl-(cyclohexyl)methanone (**6c**, 0.90 g) as a white solid in 90% isolated yield: mp 73−74 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (d, J = 5.0 Hz, 1H), 6.54 (d, J = 5.0 Hz, 1H), 5.99 (s, 1H), 4.15−4.12 (m, 2H), 4.08−4.03 (m, 2H), 3.07−3.04 (m, 1H), 1.83 (t, J = 15 Hz, 4H), 1.72 (d, J = 15 Hz, 1H), 1.51 (q, J = 15 Hz, 2H), 1.34 (q, J = 15 Hz, 2H), 1.27 (t, J = 15 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.2, 155.4, 152.5, 117.4, 110.4, 97.6, 65.5, 46.5, 29.1, 26.0, 25.9; HRMS (EI) for [$C_{14}H_{18}O_4$] calcd 250.1205, found 250.1208.

1-(5-(1,3-Dioxolan-2-yl)furan-2-yl)-2,2-dimethylpropan-1-one ***6d***. Following the general procedure, 0.80 g of **6d** was obtained as a pale yellow oil in 89% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 (d, J = 5 Hz, 1H), 6.52 (d, J = 5.0 Hz, 1H), 5.98 (s, 1H), 4.13 (q, J = 5.0 Hz, 2H0, 4.05 (q, J = 5.0 Hz, 2H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.0, 154.3, 152.6, 118.4, 109.9, 97.5, 65.5, 43.2, 26.9; GC−MS (EI, 70 eV) m/z (%) 224 (25) [M^+], 209 (4), 167 (100), 139 (86), 95 (87), 73 (53), 57 (100).

5-(1,3-Dioxolan-2-yl)furan-2-yl-(thiophen-3-yl)methanone ***6e***. Following the general procedure, 0.75 g of **6e** was obtained as a pale yellow oil in 75% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.41 (s, 1H), 7.74 (d, J = 5.0 Hz, 1H), 7.36 (d, J = 5.0 Hz, 1H), 7.30 (d, J = 5.0 Hz, 1H), 6.62 (d, J = 5.0 Hz, 1H), 6.04 (s, 1H), 4.16−4.12 (m, 2H), 4.10−4.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.4, 155.6, 153.2, 140.1, 133.9, 128.5, 126.0, 119.4, 110.6, 97.6, 65.5; GC−MS (EI, 70 eV) m/z (%) 250 (22) [M^+], 205 (17), 191 (13), 139 (100), 111 (60), 95 (26).

5-(1,3-Dioxolan-2-yl)furan-2-yl-(6-chloropyridin-3-yl)methanone ***6f***. Following the general procedure, 0.92 g of **6f** was obtained as an off-white solid in 83% isolated yield: mp 78−79 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.06 (d, J = 5.0 Hz, 1H), 8.27 (d, J = 5.0 Hz, 1H), 7.49 (dd, J = 5.0 Hz, 1H), 7.32 (d, J = 5.0 Hz, 1H), 6.67 (d, J = 5.0 Hz, 1H), 6.02 (s, 1H), 4.16−4.12 (m, 2), 4.10−4.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.1, 157.0, 155.3, 152.1, 150.9, 139.7, 131.5, 124.6, 121.2, 111.0, 97.4, 65.6; HRMS (EI) for [$C_{13}H_{10}ClNO_4$] calcd 279.0298, found 279.0299.

1-(5-(1,3-Dioxolan-2-yl)furan-2-yl)-2,2,2-trifluoroethanone ***6g***. Following the general procedure, 0.77 g of **6g** was obtained as a pale yellow oil in 65% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 (d, J = 5.0 Hz, 1H), 6.68 (d, J = 5.0 Hz, 1H), 6.02 (s, 1H), 4.10−4.12 (m, 2H), 4.08−3.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6(q), 160.1, 146.8, 124.7, 116.1 (q), 111.2, 97.1, 65.7; GC−MS (EI, 70 eV) m/z (%) 235 (15) [M-1], 191 (33), 177 (17), 139 (100), 123 (16), 95 (44), 79 (54).

2-(5-Allylfuran-2-yl)-1,3-dioxolane ***6h***. Following the general procedure, 0.63 g of **6h** was obtained as a pale yellow oil in 70% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.35 (d, J = 5.0 Hz, 1H), 5.98 (d, J = 5.0 Hz, 1H), 5.95−5.88 (m, 1H), 5.86 (s, 1H), 5.16−5.10 (m, 2H), 4.13−4.09 (m, 2H), 4.02−3.95 (m, 2H), 3.39 (d, J = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.1, 149.6, 133.6, 117.3, 109.9, 106.3, 98.0, 65.2, 32.8; GC−MS (EI, 70 eV) m/z (%) 180 (34) [M+], 139 (100), 121 (46), 95 (24), 79 (73).

2-(5-(4-Bromophenyl)furan-2-yl)-1,3-dioxolane ***a***. Following the general procedure, 1.08 g of **a** was obtained as a yellow oil in 92% isolated yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (dd, J = 10.0 Hz, 4H), 6.59 (d, J = 5.0 Hz, 1 Hz, 6.50 (d, J = 5.0 Hz, 1H), 5.96 (s, 1H), 4.15−4.13 (m, 2H), 4.03−4.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 151.2, 131.9, 129.5, 125.6, 121.6, 110.8, 106.1, 97.9, 65.3.

5-(4-Bromophenyl)furan-2-carbaldehyde ***b***. Following the general procedure, 0.89 g of **b** was obtained as a pale yellow solid in 89% isolated yield: mp 151−152 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.65 (s, 1H), 7.68 (d, J = 10.0 Hz, 2H), 7.57 (d, J = 10.0 Hz, 2H), 7.31 (d, J = 5.0 Hz, 1H), 6.84 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.4, 158.4, 152.3, 132.4, 128.1, 126.9, 124.1, 108.3; HRMS (EI) for [$C_{11}H_7O_2Br$] calcd 251.9609, found 251.9608.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sales@riekemetals.com.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Keay, B. A.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry II*; Bird, C. W., Ed.; Elsevier: New York, 1996; Vol. 2, Chapter 2.08, pp 395−436. (b) Keay, B. A. *Chem. Soc. Rev.* **1999**, *28*, 209. (c) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (d) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955. (e) Konig, B. In *Science of Synthesis*; Maas, G., Regitz, M., Eds.; Houben-Weyl Methods of Molecular Transformations, Catalory 2; Georg Thiem Verlag; New York, 2001; Vol. 9, pp 183−286.

(2) (a) Dunlop, A. P.; Peters, F. N. *The Furans*; Reinhold Publishing Corporation: New York, 1953. (b) Donnelly, D. M. S.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 4, Section 3.12

(3) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry, A Guide for the Synthetic Chemist*, 2nd Ed.; Elsevier: New York, 2007; Chapter 6.

(4) (a) Balachari, D.; Quinn, L.; O'Doherty, G. A. *Tetrahedron Lett.* **1999**, *40*, 4769. (b) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863. (c) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033.

(5) Gauthier, D. R., Jr.; Szumigala, R. H., Jr.; Dormer, P. G.; Armstrong, J. D., III; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 375.

(6) (a) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677. (b) McClure, M. S.; Roschanger, F.; Hodson, S. J.; Millar, A.; Osterhout, M. H. *Synthesis* **2001**, *11*, 1681. (c) Other example of direct coupling: Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

(7) Haner, J.; Jack, K.; Nagireddy, J.; Raheem., M. A.; Durham., R.; Tam., W. *Synthesis* **2011**, *05*, 731.

(8) Piller, F. M.; Knochel, P. *Synthesis* **2011**, *11*, 1751.

(9) For examples of using 5-bromo-2-furaldehyde for coupling reaction, see: (a) Karpov, A. S.; Rominger, F.; Muller, T. J. *J. Org. Chem.* **2003**, *68*, 1503. (b) Lewis, T. A.; Bayless, L.; Eckman, J. B.; Ellis, J. L.; Grewal, G.; Libertine, L.; Nicolas, J. M.; Scannell, R. T.; Wels, B. F.; Wenberg, K.; Wypij, D. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2265.

(10) For general procedure for organozincs, see: (a) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925. (b) Rieke, R. D.; Hanson, M. V.; Brown., J. D. *J. Org. Chem.* **1996**, *61*, 2726.

(11) (a) Manolikakes, G.; Hernandez, C. M.; Schade, M. A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 8422. (b) Manolikakes, G.; Schade, M. A.; Hernandez, C. M.; Mayr, H.; Knochel, P. *Org. Lett.* **2008**, *10*, 2765. (c) Kim, S. H.; Rieke, R. D. *Tetrahedron Lett.* **2009**, *50*, 6985.

(12) An attempt for the preparation of 3,4,5-trimethoxyphenylzinc bromide using the direct insertion of active zinc (Zn*) to the corresponding organic halide was unsuccessful. Instead, an unidentified mixture was obtained (unpublished result from our lab).