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Highly Substituted Lactone/Ester-Containing Furan Library by the Palladium-Catalyzed Carbonylation of Hydroxyl-Substituted 3-Iodofurans

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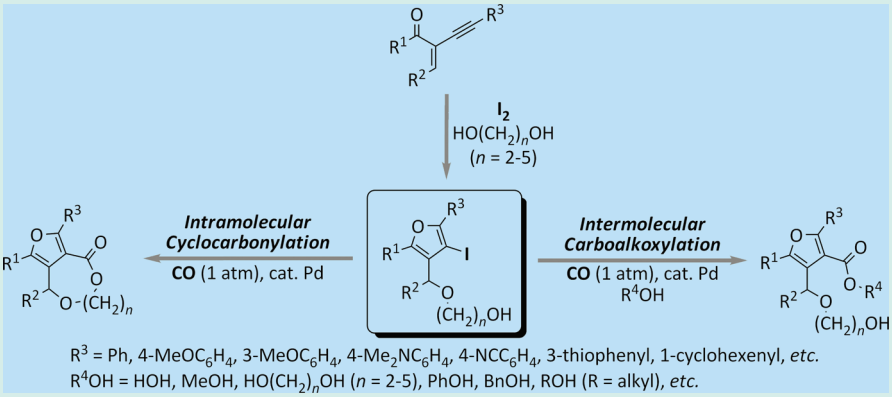
Supporting Information

ABSTRACT:



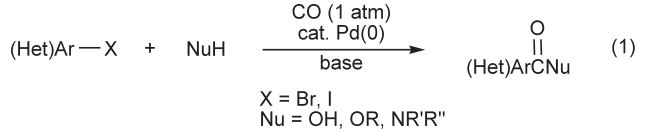
Highly substituted lactone- and ester-containing furans have been prepared by the efficient palladium-catalyzed intramolecular cyclocarbonylation or intermolecular carboalkoxylation, respectively, of hydroxyl-containing 3-iodofurans, readily prepared by the iodocyclization of 2-(1-alkynyl)-2-alken-1-ones in the presence of various diols.

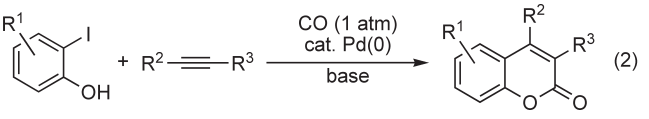
KEYWORDS: iodocyclization, nucleophile, carboalkoxylation, cyclocarbonylation, furan

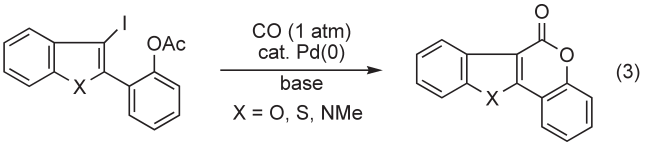
INTRODUCTION

Furans represent an important class of heterocyclic compounds as they are prevalent in many biologically active natural products, as well as numerous pharmacologically interesting compounds.[1−3] Among these, heteroatom-substituted furans represent an important subclass, both as synthons and as functionalized heterocycles of biological interest. Thus, the design and discovery of synthetic methods that provide access to highly substituted furans is an active area of investigation.[4−9]

Transition metal-catalyzed carbonylation reactions are of broad applicability, in terms of both basic research and commercial applications.[10,11] This chemistry has been widely employed in organic synthesis, because it can be utilized on a wide variety of substrates to produce a wide range of carbonyl products and it generally proceeds smoothly under low pressures of carbon monoxide (eq 1).[12,13] Similarly, the palladium-catalyzed cyclocarbonylation/lactonization of organic halides is very useful synthetic methodology that has become an important tool in organic synthesis.[14−18] For example, we have reported that the coupling of *o*-iodophenols, internal alkynes, and carbon monoxide efficiently affords 3,4-disubstituted coumarins (eq 2).[19,20] Similarly, we have prepared coumestans and coumestrol by iodocyclization and subsequent palladium-catalyzed intramolecular lactonization using an acetoxy group as the nucleophile (eq 3).[21]







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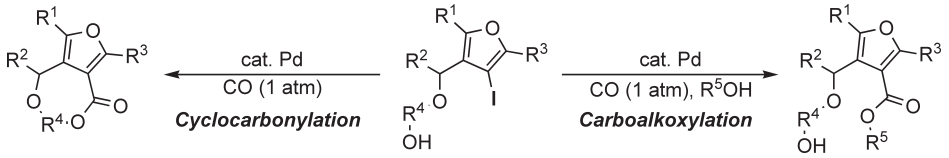
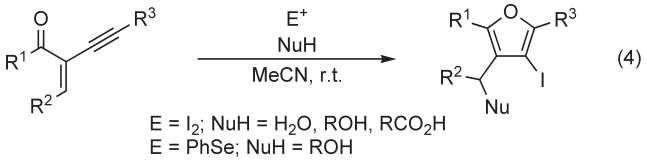
Scheme 1





Recently, we have developed an efficient synthesis of tetrasubstituted 3-iodofurans through the electrophile-induced cyclization of 2-(1-alkynyl)-2-alken-1-ones in the presence of various nucleophiles (eq 4).[5,22] These multisubstituted 3-iodofurans provide an ideal intermediate for further useful structure elaborations by a variety of C−C, C−O, C−N and C−S bond forming processes.[22−29] Thus, the carbon−halogen bond can be utilized for a variety of palladium-catalyzed reactions, including Suzuki−Miyaura,[30] Sonogashira,[31] Buchwald−Hartwig,[32,33] and Heck[12] reactions to name just a few.

As a continuation of our interest in the development of attractive strategies for the synthesis of highly substituted furans,[22] we envisioned that hydroxyl-substituted 3-iodofurans, readily available by iodocyclization in the presence of diols, should prove valuable as building blocks for combinatorial chemistry by intramolecular cyclocarbonylation, as well as intermolecular carboalkoxylation (Scheme 1).

Herein, we report an efficient method for the palladium-catalyzed intramolecular cyclocarbonylation and intermolecular carboalkoxylation of various hydroxyl-substituted 3-iodofurans to give lactone- and ester-containing furan products, respectively. The hydroxyl substituents present in the latter substrates can be critical for receptor binding in vitro because of their hydrophilicity and, thus, lipophobic nature.[34] According to calculations using Lipinski's rules,[35] terminal hydroxyl-containing furans should be good drug candidates. Intramolecular cyclocarbonylation would also appear to provide an interesting set of lactones of potential biological interest. We anticipate that this chemistry should find broad applications in synthetic organic chemistry, as well as the pharmaceutical sciences.

RESULTS AND DISCUSSION

We hypothesized that our previously described iodocyclization process should readily afford the requisite iodofurans for intramolecular cyclocarbonylation and intermolecular carboalkoxylation processes,[22] resulting in a diverse library of lactone- and ester-containing furans, respectively. A convenient two-step approach to various hydroxyl-containing 3-iodofurans **2** has been developed, which involves (i) the Sonogashira coupling of 2-iodo-2-alken-1-ones[36] with terminal alkynes and (ii) electrophilic cyclization by I_2 (Scheme 2).[5] The alkynes **1** were prepared by the palladium/copper-catalyzed Sonogashira coupling of appropriate 2-iodo-2-alken-1-ones with terminal alkynes. The results are summarized in Table 1.

As the key step in our library synthesis, various hydroxyl-substituted 3-iodofurans **2** were efficiently prepared by electrophilic

Scheme 2

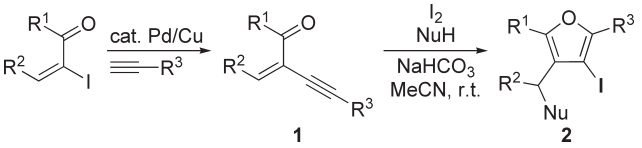
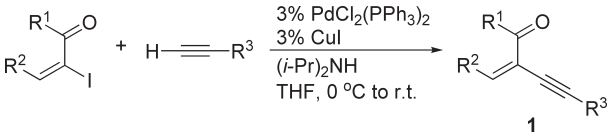
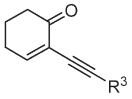
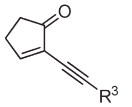
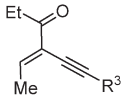


Table 1. Library Data for Compounds 1{*1*−*12*}



alkenynone **1**	R^3	yield (%)[a]
		
1{*1*}	C_6H_5	74
1{*2*}	4-$MeOC_6H_4$	91
1{*3*}	3-$MeOC_6H_4$	83
1{*4*}	4-$Me_2NC_6H_4$	75
1{*5*}	4-NCC_6H_4	90
1{*6*}	3-thiophenyl	66
1{*7*}	1-cyclohexenyl	82
		
1{*8*}	4-$MeOC_6H_4$	92
1{*9*}	4-$Me_2NC_6H_4$	85
1{*10*}	3-thiophenyl	87
		
1{*11*}	C_6H_5	66
1{*12*}	4-$MeOC_6H_4$	84

[a] All yields are isolated yields after column chromatography. The desired products **1** have been characterized by ^1H and ^{13}C NMR spectroscopy.

cyclization of the corresponding alkynes **1** with various alcohols as nucleophiles using I_2 for only 0.5 h at room temperature. The results of this iodocyclization process are summarized in Table 2 and Figure 1. All of the reactions were monitored by thin layer chromatography and the products purified by column chromatography.

The scope of this iodocyclization has been briefly examined. Alkynes bearing a phenyl substituent exhibited broad generality

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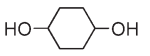
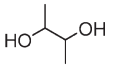
Table 2. Library Data for Hydroxyl-Containing 3-Iodofurans 2[a]

entry	1	NuH	product 2	yield (%)[b]	entry	1	NuH	product 2	yield (%)[b]
1	**1**{*1*}	$HO(CH_2)_2OH$	**2**{*1*}	83	11	**1**{*3*}	$HO(CH_2)_2OH$	**2**{*11*}	76
2	**1**{*1*}	$HO(CH_2)_3OH$	**2**{*2*}	77	12	**1**{*4*}	$HO(CH_2)_2OH$	**2**{*12*}	87
3	**1**{*1*}	$HO(CH_2)_4OH$	**2**{*3*}	56	13	**1**{*5*}	$HO(CH_2)_2OH$	**2**{*13*}	89
4	**1**{*1*}	$HO(CH_2)_5OH$	**2**{*4*}	65	14	**1**{*6*}	$HO(CH_2)_2OH$	**2**{*14*}	82
5	**1**{*1*}		**2**{*5*}	nr[c]	15	**1**{*7*}	$HO(CH_2)_2OH$	**2**{*15*}	82
6	**1**{*1*}		**2**{*6*}	nr[c]	16	**1**{*8*}	$HO(CH_2)_2OH$	**2**{*16*}	86
7	**1**{*1*}	H_2O	**2**{*7*}	79	17	**1**{*9*}	$HO(CH_2)_2OH$	**2**{*17*}	66
8	**1**{*2*}	$HO(CH_2)_2OH$	**2**{*8*}	82	18	**1**{*10*}	$HO(CH_2)_2OH$	**2**{*18*}	63
9	**1**{*2*}	$HO(CH_2)_3OH$	**2**{*9*}	67	19	**1**{*11*}	$HO(CH_2)_2OH$	**2**{*19*}	43
10	**1**{*2*}	$HO(CH_2)_5OH$	**2**{*10*}	47	20	**1**{*12*}	$HO(CH_2)_2OH$	**2**{*20*}	84

[a] Unless otherwise noted, all of the reactions have been carried out using $NaHCO_3$ (2.0 equiv), the nucleophile (4.0 equiv), and I_2 (2.0 equiv) in MeCN (0.1 M conc.) at room temperature for 0.5 h. [b] Isolated yields after column chromatography. All hydroxyl-containing 3-iodofurans **2** have been characterized by ^1H and ^{13}C NMR spectroscopy. [c] Starting material **1**{*1*} decomposed.

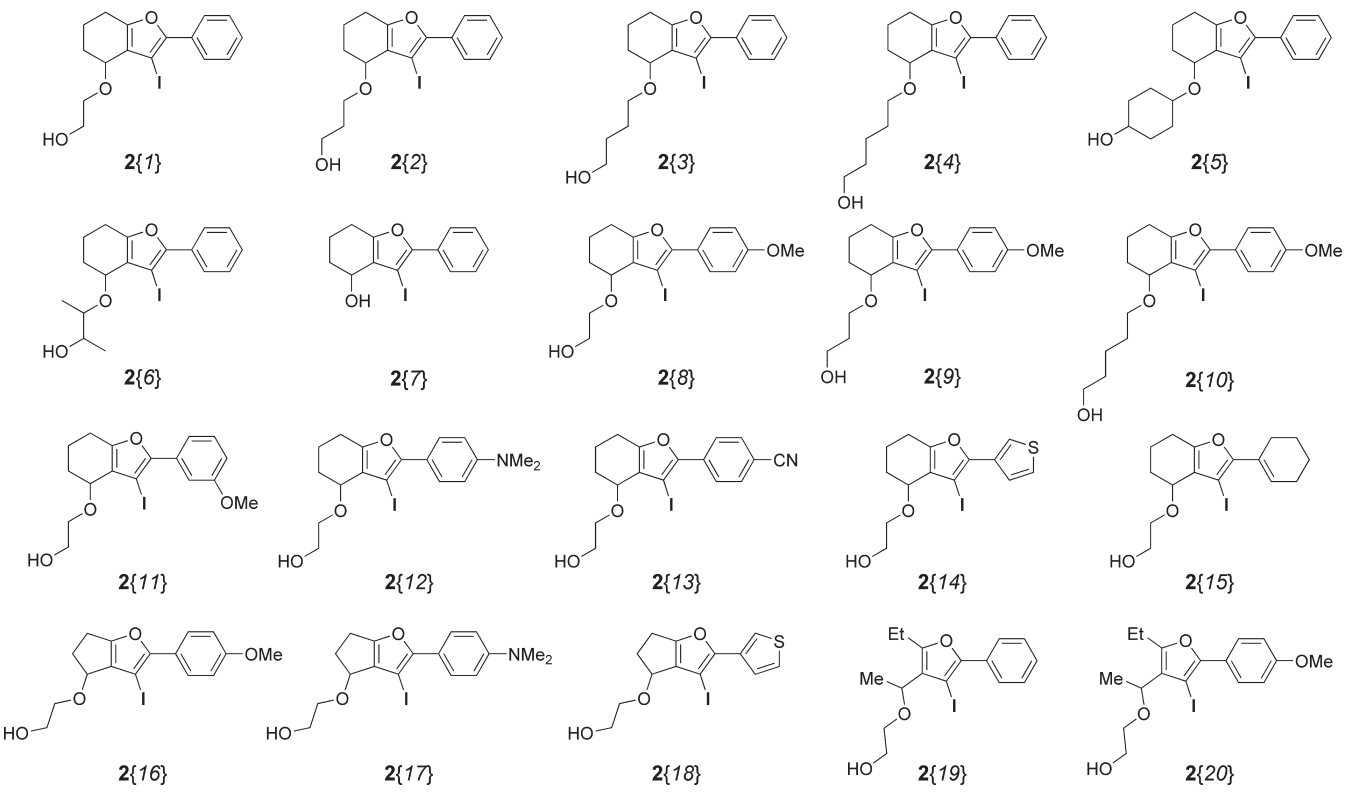


Figure 1. Hydroxyl-containing 3-iodofurans **2** synthesized by iodocyclization.

with a range of diols. With 1,2-ethanediol as the nucleophile, a high yield of iodocyclization product is obtained (Table 2, entry 1). However, when longer chain diols, such as 1,3-propanediol, 1,4-butanediol and 1,5-pentanediol, were used, somewhat lower yields were obtained (Table 2, entries 2−4). Unfortunately, none of the desired cyclized products were obtained when employing secondary diols, e.g. 1,4-cyclohexanediol and 2,3-butanediol (Table 2, entries 5 and 6). Water is a suitable nucleophile, affording the cyclized product **2**{*7*} in a high yield (Table 2, entry 7). 2-Arylethynyl-2-cyclohexen-1-ones bearing an electron-rich aromatic ring, such as those containing a methoxy group or a dimethylamino group reacted well with I_2, affording the corresponding iodofurans in good yields (Table 2; entries 8−10 and 12). Placing an electron-donating methoxy group in the position meta to the alkyne gave a 76% yield of the cyclized product **2**{*11*} (Table 2, entry 11). When the terminus of the

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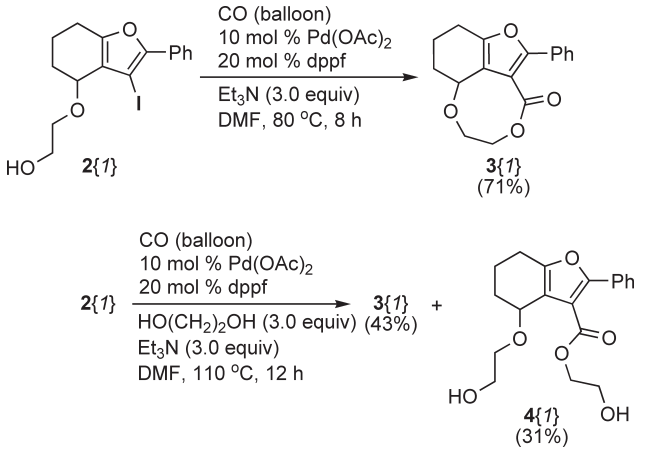
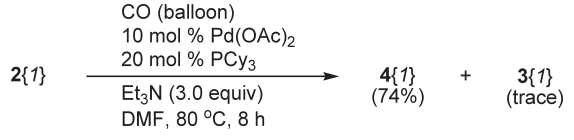
alkynyl moiety contained an aryl group bearing an electron-withdrawing group, such as a cyano group, the yield was even better (Table 2, entry 13). Products from a heterocyclic thiophenyl group and a cyclohexenyl group were also isolated in modest yields (Table 2, entries 14 and 15). Similarly, cyclized products from 2-arylethynyl-2-cyclopenten-1-ones and acyclic substrates have also been obtained in good yields (Table 2, entries 16−20).

During our investigation of the intramolecular cyclocarbonylation and intermolecular carboalkoxylation processes, we chose as our model system to examine the palladium-catalyzed reaction of hydroxyl-containing 3-iodofuran **2**{*1*} under one atmosphere of carbon monoxide pressure (Scheme 3). As predicted, hydroxyl-containing 3-iodofuran **2**{*1*} smoothly underwent intramolecular cyclocarbonylation using dppf as the ligand and triethylamine as the base in the presence of $Pd(OAc)_2$ as the catalyst and using a balloon (1 atm) of carbon monoxide to give the desired lactone **3**{*1*} in a 71% yield. Unfortunately, the carboalkoxylation of **2**{*1*} with 3.0 equiv of ethylene glycol and the same reagents at 110 °C for 12 h did not prove suitable for preparation of the desired diol **4**{*1*}, as only a 31% yield was obtained, alongside the cyclized byproduct **3**{*1*} (43% yield).

Scheme 3



Scheme 4



In preliminary studies, we examined the carboalkoxylation of hydroxyl-containing 3-iodofuran **2**{*1*} with ethylene glycol under various conditions, including various catalysts and ligands.[22] As we previously communicated, our brief ligand survey indicated that reaction efficiencies are highest when monodentate ligands, such as tricyclohexylphosphine (PCy_3), are used as the ligand and $Pd(OAc)_2$ is used as the catalyst. A 74% isolated yield of the desired product **4**{*1*} can be obtained when 20 mol % of PCy_3 is employed (Scheme 4). When optimizing the reaction, the base and solvent were held constant, while the palladium-catalyst and ligand were varied. Thus, under our optimized conditions [10 mol % $Pd(OAc)_2$, 20 mol % PCy_3, TEA (4.0 equiv), and diol (5.0 equiv) in DMF at 110 °C under 1 atm of CO], intermolecular carboalkoxylation of the hydroxyl-containing 3-iodofurans **2**{*1*} to the corresponding ester-containing furans **4**{*1*} is favored.

Having optimized the reaction conditions for the intramolecular cyclocarbonylation and intermolecular carboalkoxylation of various hydroxyl-containing 3-iodofurans **2**, we have further determined the scope of these two processes (Scheme 5 and Table 3). Neither electron-donating nor electron-deficient groups on the furan skeleton seriously affect the efficiency of these processes. The reaction has good substrate scope and tolerates a broad range of functional groups. The ability to readily accommodate Ph, $MeOC_6H_4$, $Me_2NC_6H_4$, NCC_6H_4, thiophenyl, and cyclohexenyl groups should allow one to further functionalize these products by employing standard organic synthetic methods. During the carboalkoxylation, a trace amount of cyclized lactone byproduct **3**, the intramolecular cyclocarbonylation product, have been observed. All of the structures of the compounds **3**/**4** have been confirmed by ^1H and ^{13}C NMR spectroscopy after purification by flash chromatography (see the Supporting Information).

As mentioned earlier, the carboalkoxylation product **4**{*1*} from **2**{*1*} and 1,2-ethanediol was obtained in a 74% yield (Table 3, entry 1). The carbomethoxylation of **2**{*1*} using methyl alcohol afforded the corresponding methyl ester in a 73% yield, but required a much longer reaction time (Table 3, entry 2). Use of a longer alkyl chain-containing monoalcohol, 1-pentanol, produced a 38% yield of the corresponding coupling product **4**{*3*}, which was also accompanied by the cyclized lactone **3**{*1*} in a 35% yield (Table 3, entry 3). The carboalkoxylation of **2**{*1*} using phenol afforded the desired product **4**{*4*} but in a somewhat lower yield, and this reaction required a longer reaction time (Table 3, entry 4). Similarly, using benzyl alcohol, the desired product **4**{*5*} was isolated in a 36% yield (Table 3, entry 5). Unfortunately, the product **4**{*6*} could not be isolated upon treatment with 1,4-cyclohexanediol (Table 3, entry 6). Only a small amount of the cyclized byproduct **3**{*1*} was observed.

We have also examined the effect of different alkyl-containing 3-iodofurans **2**{*1*−*4*} on the intramolecular cyclocarbonylation/lactonization process (Table 3, entries 7−10). 3-Iodofuran-containing alcohol **2**{*1*} gave the fastest lactonization, reaching

Scheme 5

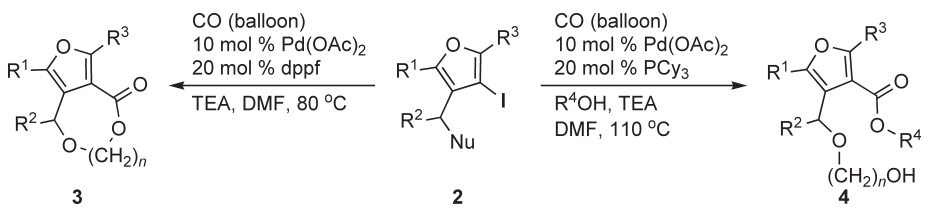


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Table 3. Intramolecular Cyclocarbonylation to 3 and Intermolecular Carboalkoxylation to 4[a]

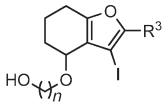
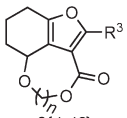
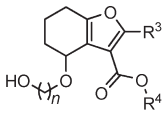
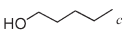
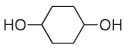
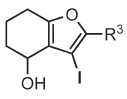
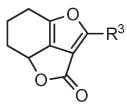
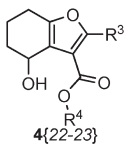
entry	3-iodofuran **2**	n	R^3	R^4OH	time (h)	product **3**	product **4**	yield (%)[b]
	 **2**{*1-4, 8-15*}					 **3**{*1-12*}	 **4**{*1-21*}	
1	**2**{*1*}	2	Ph	$HO(CH_2)_2OH$	12		**4**{*1*}	74
2	**2**{*1*}	2	Ph	CH_3OH[c]	24		**4**{*2*}	73
3	**2**{*1*}	2	Ph		24		**4**{*3*}	38[d]
4	**2**{*1*}	2	Ph	PhOH[c]	32		**4**{*4*}	27
5	**2**{*1*}	2	Ph	BnOH[c]	32		**4**{*5*}	36
6	**2**{*1*}	2	Ph		12		**4**{*6*}	nr[e]
7	**2**{*1*}	2	Ph	-	9	**3**{*1*}		77
8	**2**{*2*}	3	Ph	-	24	**3**{*2*}		47[f]
9	**2**{*3*}	4	Ph	-	48	**3**{*3*}		trace[g]
10	**2**{*4*}	5	Ph	-	48	**3**{*4*}		trace[g]
11	**2**{*8*}	2	4-$MeOC_6H_4$	-	9	**3**{*5*}		83
12	**2**{*8*}	2	4-$MeOC_6H_4$	CH_3OH[c]	24		**4**{*7*}	81
13	**2**{*8*}	2	4-$MeOC_6H_4$	$HO(CH_2)_2OH$	12		**4**{*8*}	76
14	**2**{*8*}	2	4-$MeOC_6H_4$	$HO(CH_2)_3OH$	12		**4**{*9*}	74
15	**2**{*8*}	2	4-$MeOC_6H_4$	$HO(CH_2)_4OH$	18		**4**{*10*}	68
16	**2**{*8*}	2	4-$MeOC_6H_4$	$HO(CH_2)_5OH$	18		**4**{*11*}	72
17	**2**{*9*}	3	4-$MeOC_6H_4$	-	9	**3**{*6*}		58
18	**2**{*9*}	3	4-$MeOC_6H_4$	$HO(CH_2)_2OH$	12		**4**{*12*}	76
19	**2**{*10*}	5	4-$MeOC_6H_4$	-	24	**3**{*7*}		trace[g]
20	**2**{*10*}	5	4-$MeOC_6H_4$	$HO(CH_2)_2OH$	12		**4**{*13*}	65
21	**2**{*11*}	2	3-$MeOC_6H_4$	-	9	**3**{*8*}		81
22	**2**{*11*}	2	3-$MeOC_6H_4$	CH_3OH[c]	24		**4**{*14*}	72
23	**2**{*12*}	2	4- $Me_2NC_6H_4$	-	9	**3**{*9*}		83
24	**2**{*12*}	2	4- $Me_2NC_6H_4$	CH_3OH[c]	24		**4**{*15*}	76
25	**2**{*12*}	2	4- $Me_2NC_6H_4$	$HO(CH_2)_2OH$	12		**4**{*16*}	81
26	**2**{*12*}	2	4- $Me_2NC_6H_4$	$HO(CH_2)_3OH$	12		**4**{*17*}	77
27	**2**{*13*}	2	4-NCC_6H_4	-	9	**3**{*10*}		69
28	**2**{*13*}	2	4-NCC_6H_4	$HO(CH_2)_3OH$	12		**4**{*18*}	66
29	**2**{*14*}	2	3-thiophenyl	-	9	**3**{*11*}		74
30	**2**{*14*}	2	3-thiophenyl	CH_3OH[c]	24		**4**{*19*}	68
31	**2**{*15*}	2	1-cyclohexenyl	-	9	**3**{*12*}		75
32	**2**{*15*}	2	1-cyclohexenyl	CH_3OH[c]	24		**4**{*20*}	71
33	**2**{*15*}	2	1-cyclohexenyl	$HO(CH_2)_2OH$	12		**4**{*21*}	82
	 **2**{*7*}					 **3**{*13*}	 **4**{*22-23*}	
34	**2**{*7*}	-	Ph	-	48	**3**{*13*}		nr[e]
35	**2**{*7*}	-	Ph	$HO(CH_2)_2OH$	12		**4**{*22*}	73
36	**2**{*7*}	-	Ph		16		**4**{*23*}	62

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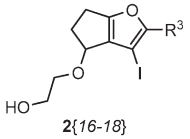
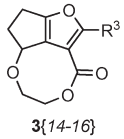
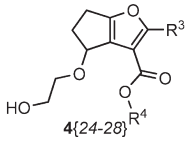
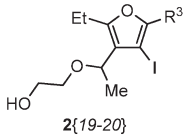
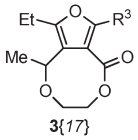
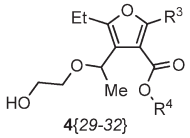
Table 3. Continued

entry	3-iodofuran **2**	n	R^3	R^4OH	time (h)	product **3**	product **4**	yield (%)[b]
	 **2**{*16-18*}					 **3**{*14-16*}	 **4**{*24-28*}	
37	**2**{*16*}	2	4-$MeOC_6H_4$	-	9	**3**{*14*}		63
38	**2**{*16*}	2	4-$MeOC_6H_4$	CH_3OH[c]	24		**4**{*24*}	52[h]
39	**2**{*16*}	2	4-$MeOC_6H_4$	$HO(CH_2)_2OH$	12		**4**{*25*}	67
40	**2**{*17*}	2	4- $Me_2NC_6H_4$	-	9	**3**{*15*}		61
41	**2**{*17*}	2	4- $Me_2NC_6H_4$	CH_3OH[c]	24		**4**{*26*}	73
42	**2**{*17*}	2	4- $Me_2NC_6H_4$	$HO(CH_2)_2OH$	12		**4**{*27*}	85
43	**2**{*18*}	2	3-thiophenyl	-	9	**3**{*16*}		68
44	**2**{*18*}	2	3-thiophenyl	CH_3OH[c]	24		**4**{*28*}	71
	 **2**{*19-20*}					 **3**{*17*}	 **4**{*29-32*}	
45	**2**{*19*}	2	Ph	$HO(CH_2)_2OH$	12		**4**{*29*}	37
46	**2**{*20*}	2	4-$MeOC_6H_4$	-	9	**3**{*17*}		66[h]
47	**2**{*20*}	2	4-$MeOC_6H_4$	CH_3OH[c]	36		**4**{*30*}	55
48	**2**{*20*}	2	4-$MeOC_6H_4$	$HO(CH_2)_2OH$	24		**4**{*31*}	64
49	**2**{*20*}	2	4-$MeOC_6H_4$	$HO(CH_2)_5OH$	24		**4**{*32*}	58

[a] Representative procedures: (i) *Intramolecular cyclocarbonylation*. The 3-iodofuran **2** (0.20 mmol), 10 mol % $Pd(OAc)_2$, 20 mol % dppf, and TEA (0.80 mmol) were stirred in DMF (2.0 mL) at room temperature. The vial was purged with CO for 2 min and then connected to a balloon of CO, and the reaction mixture was stirred at 80 °C. (ii) *Intermolecular carboalkoxylation*. The 3-iodofuran **2** (0.20 mmol), 10 mol % $Pd(OAc)_2$, 20 mol % PCy_3, TEA (0.80 mmol), and R^4OH (1.00 mmol) were stirred in DMF (2.0 mL) at room temperature. The vial was purged with CO for 2 min and then connected to a balloon of CO, and the reaction mixture was stirred at 110 °C. [b] All yields are isolated yields after column chromatography. The desired products **3** and/or **4** have been characterized by ^1H and ^{13}C NMR spectroscopy. [c] 10.0 equiv of the desired alcohol were used. [d] The cyclized byproduct **3**{*1*} was observed in 35% yield. [e] None of the desired carboalkoxylation product was observed. The starting material **2**{*1*} decomposed. [f] Some starting material remained. [g] The starting material remained. [h] An inseparable mixture was obtained.

completion in 9 h (Table 3, entry 7). The longer chain containing 3-iodofuran **2**{*2*} afforded a slightly lower yield of the desired product **3**{*2*} than **2**{*1*} and some starting material **2**{*2*} remained (Table 3, entry 8). Unfortunately, none of the desired products **3**{*3*} and **3**{*4*} could be obtained using longer reaction times, when starting from **2**{*3*} and **2**{*4*} (Table 3, entries 9 and 10). Noteworthy is the fact that the formation of long chain-containing **2**{*3*} and **2**{*4*} is more difficult than formation of **2**{*1*}. We next employed this chemistry on 3-iodofurans **2**{*8*}, **2**{*9*}, **2**{*10*}, and **2**{*11*} containing electron-donating substituents (Table 3, entries 11−22). Hydroxyl-containing 3-iodofurans bearing an electron-rich methoxyphenyl ring, such as **2**{*8*}, **2**{*9*}, and **2**{*11*}, smoothly reacted by cyclocarbonylation to give the desired lactone products **3**{*5*}, **3**{*6*}, and **3**{*8*}, respectively (Table 3; entries 11, 17, and 21). As predicted, the long chain-containing 3-iodofuran **2**{*10*} provided only a trace of **3**{*7*}, and the reaction suffered from low conversion (Table 3, entry 19). The products **4**{*7−14*} have been produced in modest yields by carboalkoxylation using various alcohols, including methanol, 1,2-ethanediol, 1,3-propanediol, 1,4-butanediol, and 1,5-pentanediol (Table 3; entries 12−16, 18, 20, and 22). 3-Iodofurans **2**{*12*} and **2**{*13*} bearing electron-deficient aromatic rings have also provided the desired intramolecular cyclization products (Table 3, entries 23 and 27) and intermolecular carboalkoxylation products (Table 3, entries 24−26 and 28). Furthermore, both the thiophene-substituted iodofuran **2**{*14*} and the cyclohexenyl-substituted iodofuran **2**{*15*} afforded the expected products in modest yields using our standard procedures (Table 3, entries 29−33). The carbonylation of 3-iodofuran **2**{*7*} by both the intramolecular cyclocarbonylation and intermolecular carboalkoxylation processes has been investigated (Table 3, entries 34−36). Compound **2**{*7*} cannot form the lactone-containing furan **3**{*13*} because of the ring strain (Table 3, entry 34). However, the carboalkoxylation of **2**{*7*} with two different alcohols produced the desired products **4**{*22*} and **4**{*23*} (Table 3, entries 35 and 36). The intramolecular cyclocarbonylation and intermolecular carboalkoxylation of the cyclopentane-containing 3-iodofurans **2**{*16*}, **2**{*17*}, and **2**{*18*} smoothly proceeded to the desired products in modest yields (Table 3, entries 37−44). Aliphatic-substituted 3-iodofurans **2**{*19*} and **2**{*20*} have also been employed in this chemistry. As expected, the desired products were produced exclusively in near quantitative yields (Table 3, entries 45−49).

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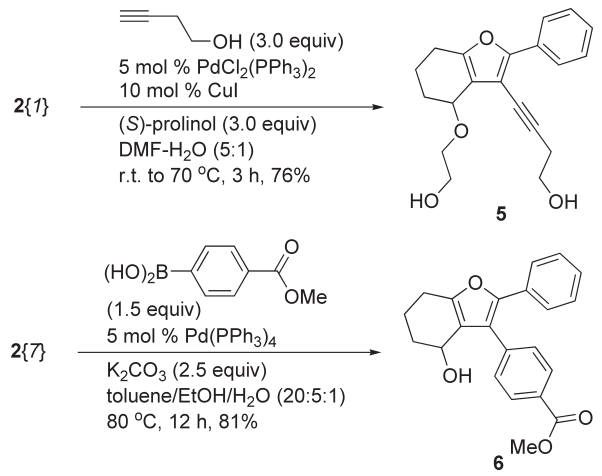
Scheme 6



The hydroxyl-containing 3-iodofurans **2** produced by this chemistry should be very useful for the synthesis of a wide variety of other substituted furans (Scheme 6) as well. For example, the Sonogashira and Suzuki−Miyaura reactions have afforded the corresponding products **5** and **6** in good yields.

In summary, we have developed a useful new synthetic route to lactone-containing furans **3** and ester-containing furans **4** by the palladium-catalyzed intramolecular cyclocarbonylation and intermolecular carboalkoxylation of hydroxyl-substituted 3-iodofurans **2**, respectively. Various hydroxyl-containing 3-iodofurans **2** have been successfully prepared through the iodocyclization of 2-(1-alkynyl)-2-alken-1-ones by I_2 in the presence of various diols. These iodine-containing furans can also be readily elaborated to more complex products using known organopalladium chemistry. The iodine-containing furans **2** have thus proven to be very useful intermediates for further diversification by known palladium-catalyzed chemistry and are thus valuable building blocks for combinatorial chemistry.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization data for all new compounds and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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