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A convenient synthetic route to furan esters and lactones by palladium-catalyzed carboalkoxylation or cyclocarbonylation of hydroxyl-substituted 3-iodofurans

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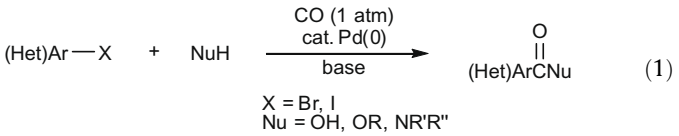
ABSTRACT

An effective palladium-catalyzed protocol for the intermolecular carboalkoxylation or intramolecular cyclocarbonylation of hydroxyl-substituted 3-iodofurans under carbon monoxide pressure has been developed. The 3-iodofurans are readily prepared by iodocyclization of 2-(1-alkynyl)-2-alken-1-ones in the presence of various diols.

Transition metal-catalyzed carbonylation is broadly applicable for the preparation of carbonyl-containing substrates, particularly the palladium-catalyzed carbonylation of organic halides.[1–6] This chemistry has found wide application in organic synthesis, because it can be employed on a wide variety of substrates to produce a wide range of carbonyl products and generally proceeds smoothly under low pressures of carbon monoxide (Eq. (1)).[7–9] Similarly, the palladium-catalyzed cyclocarbonylation/lactonization of organic halides with carbon monoxide insertion is a very useful synthetic methodology that has become an important tool in organic synthesis.[10–14]

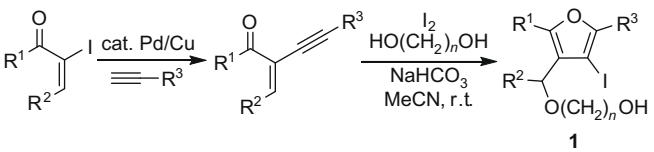


Previously, we have developed an efficient synthesis of tetrasubstituted 3-iodofurans through the electrophile-induced cyclization of 2-(1-alkynyl)-2-alken-1-ones in the presence of various nucleophiles (Scheme 1).[15] We envisioned that hydroxyl-substituted 3-iodofurans, readily available by iodocyclization in the presence of diols, should prove valuable as building blocks for combinatorial chemistry by intramolecular cyclocarbonylation, as well as intermolecular carboalkoxylation (Scheme 2).

We now wish to report an efficient method for the palladium-catalyzed intermolecular carboalkoxylation and intramolecular cyclocarbonylation of hydroxyl-substituted 3-iodofurans under one atmosphere of pressure of carbon monoxide to give lactone- and ester-containing furan products. To the best of our knowledge, the study reported here is the first general exploration of the palladium-catalyzed carboalkoxylation and cyclocarbonylation of hydroxyl-substituted 3-iodofurans.

First of all, various hydroxyl-containing 3-iodofurans **1**[16] have been readily prepared by a two-step approach involving the Sonogashira coupling of 2-iodo-2-alken-1-ones with terminal alkynes, followed by electrophilic cyclization by I_2 in the presence of diols (Scheme 1). The results of this iodocyclization process are summarized in Table 1.

To develop a general process for preparing dihydroxyfuran esters by intermolecular carboalkoxylation, we examined the carbonylation of hydroxyl-containing 3-iodofuran **1a** with ethylene glycol under various reaction conditions (Table 2). When optimizing the reaction, the base TEA and the solvent DMF were held constant, while the palladium-catalyst and ligand were varied. This decision



Scheme 1.

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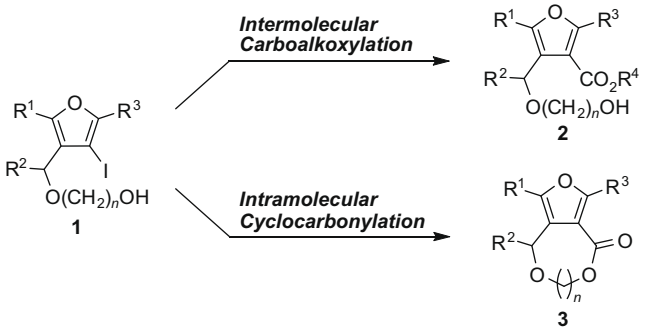


Scheme 2.

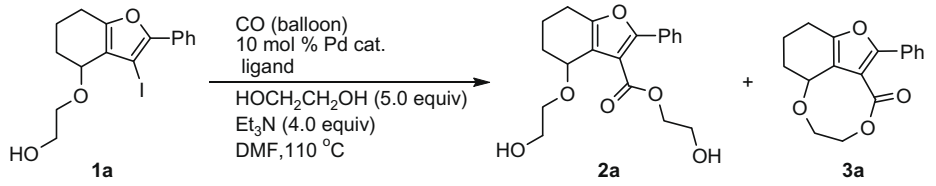
was made, because TEA and DMF have previously proven quite useful for such palladium-catalyzed carboalkoxylations.[7,8] A small amount of the desired product **2a** (<5% yield) was obtained by employing 10 mol % $Pd(OAc)_2$ with no ligand, ethylene glycol (5.0 equiv), and TEA (4.0 equiv) at 110 °C for 72 h. Under these conditions, the lactone **3a** (58%) was favored (Table 2, entry 1). We subsequently added various bidentate phosphine ligands, such as 1,1′-bis(diphenylphosphino)ferrocene (dppf, L1), bis(diphenylphosphino)methane (dppm, L2), and 1,4-bis(diphenylphosphino)butane (dppb, L3), in the hope of stabilizing the anticipated cationic palladium(II) intermediate. This significantly affected both intermolecular carboalkoxylation, as well as the intramolecular cyclocarbonylation, with diol **2a** now being the major product (Table 2, entries 2-4). (±)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine) [(±)-BINAP, L4] produced both the desired product **2a** and the by-product **3a** in poor yields (Table 2, entry 5). Interestingly, the addition of monodentate ligands, such as tricyclohexylphosphine (PCy_3, L5), triphenylphosphine (PPh_3, L6), and tris(2,6-dimethoxyphenyl)phosphine (L7), afforded an increase in the yields of ester **2a** (Table 2, entries 6–9). A 74% isolated yield of the desired product **2a** can be obtained when 20 mol % of PCy_3 (L5) is employed (Table 2, entry 7). Other phosphine ligands, such as 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos, L8) and tri-*tert*-butylphosphine, introduced as the corresponding tetrafluoroborate salt (L9), produced both the desired product **2a** and the

Table 1
Synthesis of hydroxyl-containing 3-iodofurans **1** by iodocyclization[a]

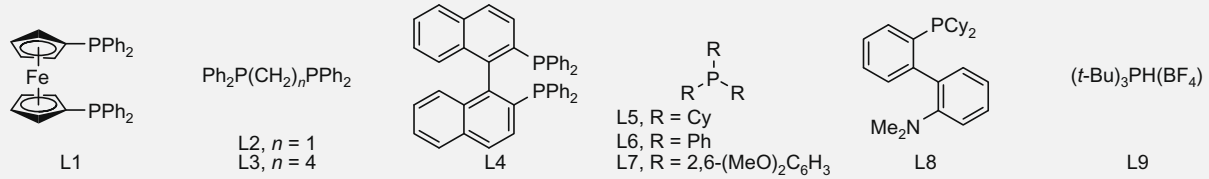
Entry	Substrate (R^3)	3-Iodofuran **1**	Yield[b] (%)
1	Ph	**1a** (n = 2)	83
2	4-$MeOC_6H_4$	**1b** (n = 2)	82
3	Ph	**1c** (n = 3)	77
4	Ph	**1d** (n = 5)	65
5	(PMP: 4-$MeOC_6H_4$)	**1e**	86

[a] Unless otherwise noted, all the reactions have been carried out using $NaHCO_3$ (2.0 equiv), the diol (4.0 equiv), and I_2 (2.0 equiv) in MeCN (0.1 M concn) at room temperature for 0.5 h.
[b] Isolated yields after column chromatography.

Table 2
Carboalkoxylation of 3-iodofuran **1a** and 1,2-ethanediol: a survey of reaction conditions[a]



Entry	Pd cat	Ligand (mol %)	Time (h)	Yield of **2a**[b] (%)	Yield of **3a**[b] (%)
1	$Pd(OAc)_2$	—	72	<5	58
2	$Pd(OAc)_2$	L1 (10)	12	38	27
3	$Pd(OAc)_2$	L2 (10)	24	58	13
4	$Pd(OAc)_2$	L3 (10)	24	48	21
5[c]	$Pd(OAc)_2$	L4 (10)	24	<5	17
6	$Pd(OAc)_2$	L5 (10)	12	68	7
7	**$Pd(OAc)_2$**	**L5 (20)**	**12**	**74**	**<5**
8	$Pd(OAc)_2$	L6 (20)	12	47	21
9	$Pd(OAc)_2$	L7 (20)	12	63	18
10[c]	$Pd(OAc)_2$	L8 (10)	12	27	23
11[c]	$Pd(OAc)_2$	L9 (10)	12	31	28
12	$PdCl_2(PPh_3)_2$	L5 (20)	24	26	53
13[c]	$PdCl_2(PPh_3)_2$	—	24	<5	37



[a] Reaction conditions: 3-iodofuran **1a** (0.20 mmol), 10 mol % Pd catalyst, 20 mol % ligand, CO (1 atm), TEA (0.80 mmol), and ethylene glycol (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] Isolated yields based on **1a**.
[c] The starting material **1a** was recovered.

cyclized lactone **3a** (Table 2, entries 10 and 11). Another palladium catalyst, $PdCl_2(PPh_3)_2$, favored the cyclized lactone product **3a** (53%), alongside a 26% yield of the diol product **2a** (Table 2, entry 12). Very little of the desired diol **2a** was obtained in the absence of added ligand (Table 2, entry 13).

Our brief ligand survey indicated that the yield of diol-containing ester **2a** is highest when PCy_3 (L5) is used as the ligand and $Pd(OAc)_2$ as the catalyst. 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], the carbonylation of hydroxyl-containing 3-iodofuran **1a** favors intermolecular carboalkoxylation to give the corresponding ester-containing furan **2a**.

Having optimized the reaction conditions for both intermolecular and intramolecular carbonylation, we have further determined the scope of these processes (Scheme 2). However, lactone formation was not examined intensively. Formation of the carboalkoxylation coupling product **2a** from **1a** and 1,2-ethanediol proceeded in a 74% yield (Table 3, entry 1).[17] During carboalkoxylation, a trace

Table 3
Intermolecular carboalkoxylation to **2** and intramolecular cyclocarbonylation to **3**[a]

Entry	3-Iodofuran **1**	R^4OH	Time (h)	Product **2**/**3**	Yield[b] (%)
1	**1a** (R^3 = Ph)	$HO(CH_2)_2OH$	12	**2a**	74
2	**1a**	CH_3OH[c]	24	**2b**	73
3	**1a**	HO *c*	24	**2c**	38
4	**1b** (R^3 = 4-$MeOC_6H_4$)	$HO(CH_2)_2OH$	12	**2d**	76
5	**1a**	—	9	**3a**	77
6	**1c**	—	24	**3b**	47[d]
7	**1d**	—	48	**3c**	Trace[e]
8	**1e**	—	9	**3d**	63
9	**1e**	$HO(CH_2)_2OH$	12	**2e**	67

[a] Representative procedure: (i) *Intermolecular carboalkoxylation*: the 3-iodofuran **1** (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. (ii) *Intramolecular cyclocarbonylation*: the 3-iodofuran **1** (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.

[b] All yields are isolated yields after column chromatography. The desired products **2** and **3** have been characterized by ^1H and ^{13}C NMR spectroscopy.

[c] 10.0 equiv of the desired alcohol were used.

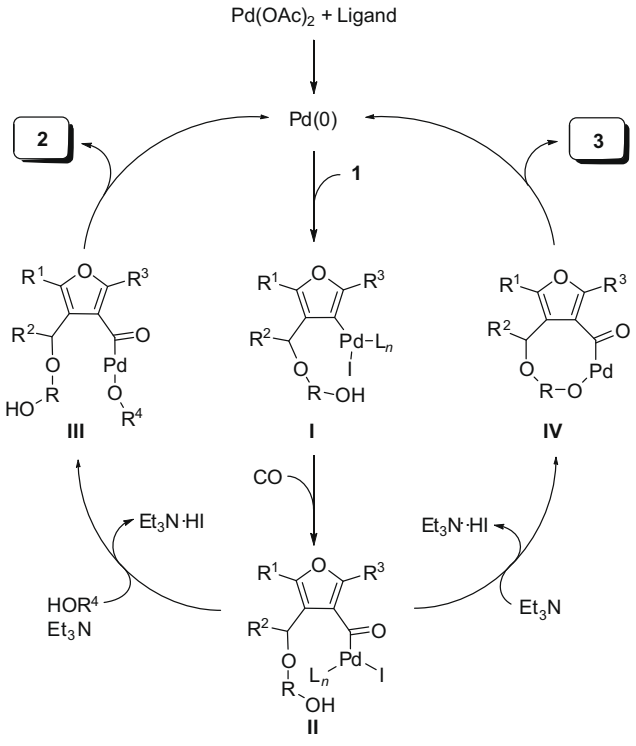
[d] Some starting material remained.

[e] Starting materials remained.

amount of cyclized by-product **3**, the intramolecular cyclocarbonylation product, was observed. The carbomethoxylation of **1a** using 10 equiv of methyl alcohol was achieved in 73% yield, but required a much longer reaction time (Table 3, entry 2). Use of a longer alkyl chain-containing monoalcohol, 1-pentanol, produced 38% of the corresponding ester **2c**, which was also accompanied by the lactone **3a** in 35% yield (Table 3, entry 3). Hydroxyl-containing 3-iodofurans bearing an electron-rich 4-methoxyphenyl ring, **1b**, smoothly react by carboalkoxylation to give the desired product **2d** (Table 3, entry 4).

We have also examined the intramolecular cyclocarbonylation/lactonization of different alkyl chain-containing 3-iodofurans **1a**, **1c**, and **1d** (Table 3, entries 5–7). 3-Iodofuran **1a** gave the fastest lactonization, reaching completion in 9 h (Table 3, entry 5).[18] Longer chain containing 3-iodofuran **1c** afforded a slightly lower yield of the desired lactone **3b** than **1a** and some starting material **1c** remained (Table 3, entry 6). Unfortunately, the desired lactone **3c** could not be obtained using longer reaction times, when starting from **1d** (Table 3, entry 7). The formation of long chain-containing **1d** is also more difficult than the formation of **1a**. The intramolecular cyclocarbonylation of cyclopentane-containing 3-iodofuran **1e** afforded the desired lactone **3d** in a decent yield (Table 3, entry 8). Similarly, the intermolecular carboalkoxylation of cyclopentane-containing 3-iodofuran **1e** smoothly proceeded to the desired product **2e** in a modest yield (Table 3, entry 9).

The selectivity of these carbonylation processes suggests the mechanism depicted in Scheme 3. Oxidative addition of the carbon–iodine bond of the 3-iodofuran **1** to Pd(0), generated in situ from PdL_n, results in the corresponding Pd(II) intermediate **I**. Carbon monoxide insertion into the carbon–palladium bond of **I** affords the acylpalladium iodide complex **II**. When alcohols (R^4OH) are used, nucleophilic attack of the hydroxyl group from the alcohol on the acyl group of the acylpalladium intermediate **II** apparently terminates the base-catalyzed cycle, affording the ester products **2** with simultaneous regeneration of the Pd(0) catalyst. On the other hand, base-catalyzed intramolecular cyclization of **II** gives a palladacycle **IV**, which undergoes reductive elimination affording cyclized product **3**.



Scheme 3.

In summary, we have developed an effective Pd-catalyzed protocol for the intermolecular carboalkoxylation of hydroxyl-substituted 3-iodofurans **1** leading to the corresponding ester-containing furans **2**, as well as intramolecular cyclocarbonylation of **1** leading to the corresponding lactone-containing furans **3**. The starting iodine-containing furans **1** have proven to be very useful intermediates for further diversification by known palladium-catalyzed chemistry, and are thus valuable building blocks for combinatorial chemistry.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.108.

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16. *General procedure for iodocyclization*: The iodofurans **1** were prepared by a modification of our earlier literature procedure.[15] To a mixture of the 2-(1-alkynyl)-2-alken-1-one (2.0 mmol), I_2 (4.0 mmol), and $NaHCO_3$ (4.0 mmol) was added a solution of the appropriate diol (8.0 mmol) in MeCN (20 mL). The resulting mixture was stirred at room temperature for 0.5 h, unless otherwise specified. The reaction was monitored by TLC to establish completion. The mixture was diluted with EtOAc (250 mL). The excess I_2 was removed by washing with satd aq $Na_2S_2O_3$. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel using EtOAc/hexanes as the eluent system. *Compound* **1a**: the product was obtained as a yellow oil (83% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 1.51–1.63 (m, 1H), 1.78–1.90 (m, 1H), 1.91–2.04 (m, 1H), 2.06–2.17 (m, 1H), 2.41–2.60 (m, 2H), 2.62–2.76 (m, 1H), 3.61–3.71 (m, 1H), 3.69–3.82 (m, 3H), 4.26 (br s, 1H), 7.21–7.32 (m, 1H), 7.38 (t, J = 7.8 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 23.3, 27.2, 62.2, 64.9, 70.5, 71.3, 123.2, 126.2 (×2), 128.0, 128.4 (×2), 130.4, 150.3, 154.1; HRMS calcd for $C_{16}H_{17}IO_3$ [M^+], 384.0222, found 384.0228.
17. *General procedure for intermolecular carboalkoxylation*: A stirred mixture of the appropriate hydroxyl-substituted 3-iodofuran **1** (0.10 mmol), 10 mol % $Pd(OAc)_2$, 20 mol % PCy_3, TEA (0.40 mmol), and excess R^4OH (0.50–1.0 mmol) in DMF (2.0 mL) was charged into a 50 mL long flask at room temperature. The mixture was flushed with CO gas for 2 min, and the flask was fitted with a balloon of CO gas. The reaction mixture was heated at 110 °C with vigorous stirring. Upon cooling to room temperature, the resulting reaction mixture was extracted with EtOAc (2 × 20 mL). The separated organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude

product was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the corresponding products **2**. *Compound* **2a**: the product was obtained as a yellow oil (74% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59–1.70 (m, 1H), 1.81–1.93 (m, 1H), 1.96–2.10 (m, 1H), 2.12–2.22 (m, 1H), 2.48 (br s, 1H), 2.50–2.63 (m, 1H), 2.66–2.78 (m, 1H), 3.10 (br s, 1H), 3.59–3.66 (m, 1H), 3.69–3.83 (m, 5H), 4.20–4.30 (m, 1H), 4.33–4.42 (m, 1H), 4.84 (br s, 1H), 7.37–7.47 (m, 3H), 7.68–7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 23.3, 27.1, 61.1, 62.3, 66.7, 69.9, 70.4, 112.6, 119.1, 128.2 (×2), 128.9 (×2), 129.6, 130.6, 154.1, 157.5, 164.4; HRMS calcd for $C_{19}H_{22}O_6$ [M^+], 346.1416, found 346.1423.

18. *General procedure for intramolecular lactonization*: A stirred mixture of the appropriate hydroxyl-substituted 3-iodofuran **1** (0.10 mmol), 10 mol % $Pd(OAc)_2$, 20 mol % dppf, and TEA (0.40 mmol) in DMF (2.0 mL) was added to a 50 mL long flask at room temperature. The mixture was flushed with CO gas for 2 min, and the flask was fitted with a balloon of CO gas. The reaction mixture was heated at 70–80 °C with vigorous stirring for 8 h. Upon cooling to room temperature, the resulting reaction mixture was extracted with EtOAc (2 × 20 mL). The separated organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the corresponding lactone **3**. *Compound* **3a**: the product was obtained as a pale yellow oil that solidified upon standing to afford an ivory solid (77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65–1.77 (m, 1H), 1.90–2.00 (m, 1H), 2.03–2.15 (m, 2H), 2.55–2.66 (m, 1H), 2.73–2.83 (m, 1H), 3.98–4.06 (m, 1H), 4.09–4.17 (m, 1H), 4.29–4.38 (m, 2H), 4.53–4.61 (m, 1H), 7.33–7.47 (m, 3H), 7.90 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 23.1, 30.9, 69.6, 71.3, 71.4, 111.4, 119.7, 126.9 (×2), 128.8 (×2), 129.3, 129.4, 152.7, 155.5, 166.8; HRMS calcd for $C_{17}H_{16}O_4$ [M^+], 284.1049, found 284.1053.