Palladium-Catalyzed Cyclocarbonylation of *o*-Iodophenols and 2-Hydroxy-3-iodopyridine with Heterocumulenes: Regioselective Synthesis of Benzo[*e*]-1,3-oxazin-4-one and Pyrido[3,2-*e*]-1,3-oxazin-4-one Derivatives

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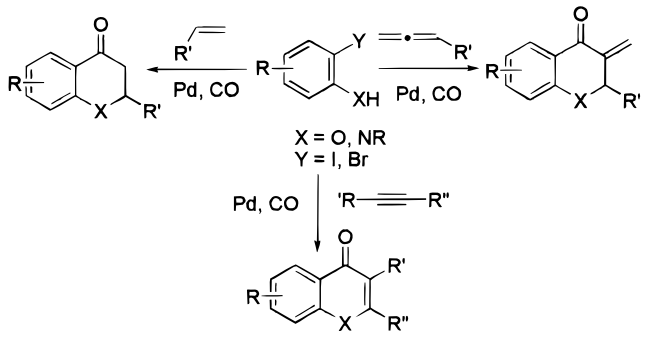
Benzo[*e*]-1,3-oxazin-2-imine-4-ones (**3**) were synthesized by cyclocarbonylation of *o*-iodophenols with carbodiimides in the presence of a catalytic amount of a palladium catalyst and 1,4-bis-(diphenylphosphino)butane under CO pressure. Product yields are dependent on the nature of the substrate, catalyst, solvent, and base as well as phosphine ligand. Reaction of *o*-iodophenols with unsymmetrical carbodiimides affords benzo[*e*]-1,3-oxazin-2-imine-4-ones (**11a**−**g**) in good yield and usually in a completely regioselective manner. Benzo[*e*]-1,3-oxazin-2,4-diones (**5**) were obtained in good to excellent yields using the same procedure and a 1:2 ratio of *o*-iodophenol/isocyanate. Pyrido-[*3,2-e*]-1,3-oxazin-4-ones (**16**) were isolated in fine yield using 2-hydroxy-3-iodopyridine instead of an iodophenol as reactant. The reaction mechanism is believed to involve in situ formation of a carbamate ester followed by palladium-catalyzed carbonylative amidation.

Introduction

The palladium-catalyzed carbonylation of aryl halides is an important, convenient, and highly effective method for the synthesis of aromatic-containing carbonyl compounds.[1] The reactions are well established to proceed by initial oxidative addition of palladium(0) to a carbon−halogen bond, followed by carbon monoxide insertion. There are many publications on the inter- and intramolecular palladium-catalyzed cross-coupling reactions of aromatic halides with a variety of unsaturated compounds [e.g., olefins,[2] alkynes,[3] and allenes[4] (Scheme 1)].

Scheme 1



We previously reported the use of heterocumulenes such as carbodiimides and isocyanates in cycloaddition ring-expansion reactions catalyzed by palladium complexes.[5] Palladium-catalyzed ring opening of vinyloxiranes[5a,b] and vinyloxetanes[5c] resulted in the formation of π-allylpalladium intermediates containing an anionic oxygen moiety. Nucleophilic addition of the anion to the carbon of the heterocumulene, followed by nucleophilic addition on the π-allyl palladium moiety, afforded heterocyclic compounds (Scheme 2).

To our knowledge, no carbonylative coupling reactions have been described of aromatic halides with cumulenes containing heteroatoms when catalyzed by transition metal complexes. We reasoned that *o*-iodophenols could undergo palladium catalyzed cyclocarbonylation with

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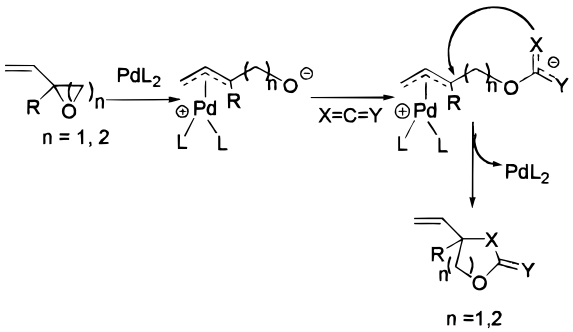
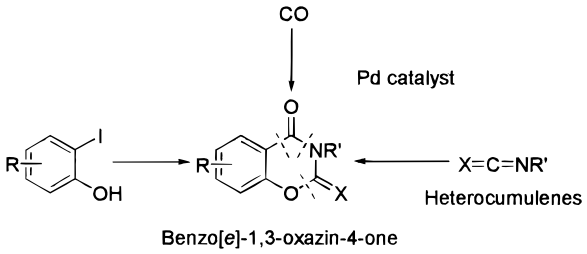
Scheme 2



Scheme 3



heterocumulenes to form benzo[*e*]-1,3-oxazin-4-ones and their derivatives (Scheme 3). These types of compounds are reported to have pharmaceutically interesting properties; for example, compounds of class **I** have potential analgesic properties[6] while **II** are effective against serine proteases[7] such as trypsin, thrombin, and plasmin (Figure 1).

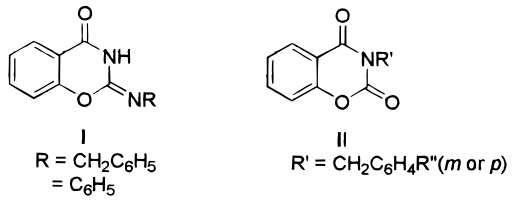


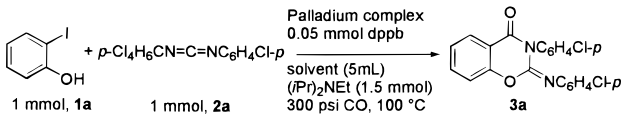
Figure 1. Structure of pharmaceutically active benzo[*e*]-1,3-oxazin-4-one derivatives.

Herein, we describe a simple and novel method for the synthesis of benzo[*e*]-1,3-oxazin-4-ones and benzo[*e*]-1,3-oxazin-2-imine-4-ones by palladium-catalyzed cyclocarbonylation of *o*-iodophenols with heterocumulenes. The anticipated products are formed in excellent yields and regioselectivity. Application of this strategy to the reaction of 2-hydroxy-3-iodopyridine with carbodiimides affords pyrido[3,2-*e*]-1,3-oxazin-2-imin-4-ones.

Results and Discussion

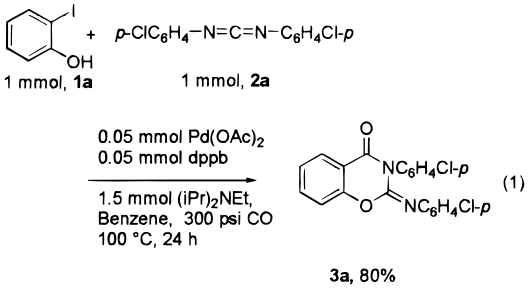
We started our investigation by treatment of *o*-iodophenol (**1a**, R = H) with bis (*p*-chlorophenyl)carbodiimide (**2a**) using reaction conditions similar to those previously reported by one of us[8] for the carbonylation of *o*-iodophenols with allenes. The palladium(0)−1,4-bis(diphenylphosphino)butane (dppb) catalyst system was generated in situ by the reaction of 0.05 mmol of $Pd(OAc)_2$ with 1 equiv of dppb in anhydrous benzene. After the mixture was stirred under N_2 at room temperature for 15 min, 1 mmol each of **1a** and **2a** and 1.5 mmol of $(i\text{-Pr})_2NEt$ were added, and the reaction mixture was stirred at 100 °C under 300 psi carbon monoxide for 24 h, resulting in the formation of *N*-(*p*-chlorophenyl)-3-(*p*-chlorophenyl)benzo-[*e*]-1,3-oxazin-2-imin-4-one (**3a**) in 80% isolated yield (eq 1).

Table 1. Effect of Solvent on the Cyclocarbonylation of *o*-Iodophenol (1a) with Bis(*p*-chlorophenyl)carbodiimide (2a) in the Presence of a Palladium Complex and dppb[a]



		isolated yield of **3a**[b] (%)	
entry	solvent	0.05 mmol of $Pd(OAc)_2$ and 0.05 mmol of dppb[c]	0.05 mmol of $Pd_2(dba)_3{\cdot}CHCl_3$ and 0.05 mmol of dppb[d]
1	benzene	80	81
2	THF	69	82
3	DME	36	77
4	DMF	61	35

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), $(i\text{-Pr})_2NEt$ (1.5 mmol), solvent (5 mL), CO (300 psi), 100 °C. [b] Isolated yield. [c] Reaction time was 24 h. [d] Reaction time was 48 h.



The influence of palladium complex, solvent, base, and substrate/catalyst ratio was then investigated. When $Pd_2(dba)_3{\cdot}CHCl_3$ (0.025 mmol) was used instead of $Pd(OAc)_2$, 81% of **3a** was obtained; however, the complete conversion of the carbodiimide required 48 h. Benzene proved to be the best solvent for the reaction (Table 1) utilizing $Pd(OAc)_2$ (entry 1), whereas THF, benzene, and DME gave similar results for $Pd_2(dba)_3{\cdot}CHCl_3$ (entries 1−3). Note that, of course, no carbonyl-containing products were detected when palladium-catalyzed reaction was run in the absence of carbon monoxide. The *o*-iodophenol (**1a**) was recovered unchanged, and the carbodiimide gave a mixture of unidentified products.

Table 2 shows the influence of different bases on the reactions. Using $Pd(OAc)_2$ as the catalyst, diisopropylethylamine was the best base (entry 1, Table 2), while K_2CO_3 was superior when using $Pd_2(dba)_3{\cdot}CHCl_3$ (entry 6). Cycloaddition of *o*-iodophenol (**1a**) with **2a** proceeds using other bases such as Et_3N, pyridine, Proton Sponge, and Na_2CO_3, but in lower product yields (entries 2−5).

Slightly lower yields of **3a** were obtained in the reaction of **1a** with **2a** and K_2CO_3 under 300 psi CO in the presence of 2.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ in THF using dppp (94%), dppe (91%), PPh_3 (95%), or PCy_3 (84%) compared with the same reaction employing dppb (96%) as the added ligand. Performing the reaction using only 2.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and in the absence of phosphine ligand afforded 62% of **3a**.

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Table 2. Effect of Base on the Cyclocarbonylation of *o*-Iodophenol (1a) with Bis(*p*-chlorophenyl)carbodiimide (2a) in the Presence of a Palladium Complex and dppb[a]

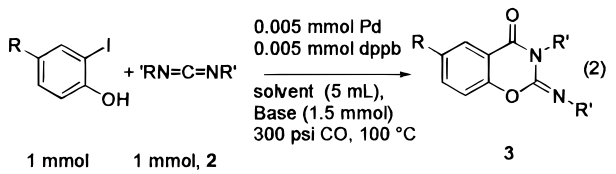
		isolated yield of **3a** (%)[b]	
entry	base	0.05 mmol of $Pd(OAc)_2$ and 0.05 mmol of dppb in benzene[c]	0.05 mmol of $Pd_2(dba)_3{\cdot}CHCl_3$ and 0.05 mmol of dppb in THF[d]
1	$(i\text{-Pr})_2NEt$	**80**	81
2	NEt_3	38	65
3	pyridine	60	80
4	Proton Sponge	46	67
5	Na_2CO_3	47	92
6	K_2CO_3	34	**96**

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), base (1.5 mmol), solvent (5 mL), CO (300 psi), 100 °C. [b] **3a** was purified by SiO_2 column Chromatography. [c] Reaction time was 24 h. [d] Reaction time was 48 h.

The results in Table 3 show that **3a** was obtained in 70−76% yield at a 500−1000:1 ratio of **1a** and **2a**/palladium catalyst (Table 3, entries 5 and 6). Isolated yields of **3a**, of at least 90%, resulted using a 20−250/1 ratio of **1a**/$Pd_2(dba)_3{\cdot}CHCl_3$ (entries 1−4). Somewhat lower yields were obtained with $Pd(OAc)_2$ as catalyst. A ratio of 200/1 was used for subsequent experiments.

As a consequence of the above results, the best reaction conditions for the cyclocarbonylation of *o*-iodophenols (**1**) with heterocumulenes involve use of 1 mmol each of **1** and **2**, 1.5 mmol of base [$(i\text{-Pr})_2EtN$, for $Pd(OAc)_2$), K_2CO_3 for $Pd_2(dba)_3{\cdot}CHCl_3$)], 0.005 mmol Pd, and 1 equiv of dppb relative to palladium in THF. Benzene was used as the solvent for $Pd(OAc)_2$.

A series of carbodiimides (**2**) were used for the Pd-catalyzed cyclocarbonylation reaction with *o*-iodophenols (**1**) (eq 2). The reactions were stirred at 100 °C under 300 psi CO, and after complete conversion of carbodiimide, the reaction mixture was purified affording **3** in good to excellent yields (Table 4).



1 mmol
1a, R = H
1b, R = CH_3
1c, R = Cl

1 mmol, **2**
2a, R' = *p*-ClC_6H_4
2b, R' = *p*-$CH_3C_6H_4$
2c, R' = C_6H_5
2d, R' = *p*-BrC_6H_4
2e, R' = *p*-$CH_3OC_6H_4$
2f, R' = C_6H_{11}
2g, R' = $^iC_3H_7$

o-Iodophenols bearing either electron-donating (R = CH_3) or electron-withdrawing (R = Cl) substituents on the aromatic ring were converted to **3** in good yields. 4-Methyl-2-iodophenol (**1b**) reacted with heterocumulenes in an analogous manner to **1a** giving rise to the anticipated heterocycles in high isolated yields (Table 4, entries 3, 7, 11, 17, and 19). When 4-chloro-2-iodophenol (**1c**) was used as the substrate, oxidative addition of palladium occurred only into the C−I bond (not C−Cl) to form **3** in high yield (entries 4, 8, 18, and 21).

When diarylcarbodiimides (**2a**−**e**) were utilized for the reaction, $Pd_2(dba)_3{\cdot}CHCl_3$ afforded **3** in higher yields than $Pd(OAc)_2$. The reverse is true (i.e., $Pd(OAc)_2$ gives **3** in higher yields than $Pd_2(dba)_3{\cdot}CHCl_3$) utilizing dialkylcarbodiimides (**2f** and **2g**). Furthermore, for the reactions using **2f** and **2g**, 2.5 mol % of palladium catalyst was needed since the reaction proceeded very slowly when 0.25 mol % of Pd was used, resulting in low product yields.

Table 3. Determination of the Optimum Amount of Palladium Catalyst Required for the Cyclocarbonylation of *o*-Iodophenol (1a) and with Bis(*p*-chlorophenyl)Carbodiimide (2a) in the Presence of 1:1 $Pd_2(dba)_3{\cdot}CHCl_3$/dppb[a]

entry	ratio of substrate/palladium catalyst	% isolated yield of **3a**[b]
1	20:1 (0.05 mmol Pd)	96 (80)[c]
2	100:1 (0.01 mmol Pd)	94 (87)[c]
3	172.5:1 (0.006 mmol Pd)	94
4	250:1 (0.004 mmol Pd)	90
5	500:1 (0.002 mmol Pd)	76
6	1000:1 (0.001 mmol Pd)	70

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), base (1.5 mmol), solvent (5 mL), CO (300 psi), 100 °C, 48 h. [b] **3a** was purified by SiO_2 column chromatography. [c] Isolated yield of **3a** from the reaction using Pd $(OAc)_2$-dppb after 24 h.

Table 4. Cyclocarbonylation of *o*-Iodophenols (1) with Carbodiimides (2) Catalyzed by a Palladium Complex and dppb[a]

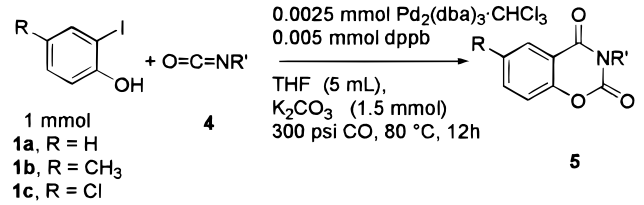
entry	**1**	R′N=C=NR′, **2**	product	catalyst[b] (mmol)	isolated yield of **3**[f] (%)
1	**1a**	**2a**	**3a**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0025)	96
2	**1a**	**2a**	**3a**	$Pd(OAc)_2$ (0.005)	80
3	**1b**	**2a**	**3b**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0025)	94
4	**1c**	**2a**	**3c**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0025)	89
5	**1a**	**2b**	**3d**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0025)	96
6	**1a**	**2b**	**3d**	$Pd(OAc)_2$ (0.005)	85
7	**1b**	**2b**	**3e**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0025)	95
8	**1c**	**2b**	**3f**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0025)	95
9	**1a**	**2c**	**3g**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0025)	95
10	**1a**	**2c**	**3g**	$Pd(OAc)_2$ (0.005)	45
11	**1b**	**2c**	**3h**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0025)	90
11	**1a**	**2d**	**3i**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0025)	94
12	**1a**	**2d**	**3i**	$Pd(OAc)_2$ (0.005)	78
13	**1a**	**2e**	**3j**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0025)	62
14	**1a**	**2e**	**3j**	$Pd(OAc)_2$ (0.005)	10
15	**1a**	**2f**	**3k**	$Pd(OAc)_2$ (0.025)[c]	93
16	**1a**	**2f**	**3k**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0125)[d]	66
17	**1b**	**2f**	**3l**	$Pd(OAc)_2$ (0.025)[e]	93
18	**1c**	**2f**	**3m**	$Pd(OAc)_2$ (0.025)[e]	93
19	**1b**	**2g**	**3n**	$Pd(OAc)_2$ (0.025)[e]	94
20	**1b**	**2g**	**3n**	$Pd_2(dba)_3{\cdot}CHCl_3$(0.0125)[d]	57
21	**1c**	**2g**	**3o**	$Pd(OAc)_2$(0.025)[e]	91

[a] Reaction conditions: refer to the Experimental Section for the General Procedure for the Cyclocarbonylation of *o*-Iodophenols (**1**) with Carbodiimides (**2**). [b] Reaction time was 48 h for $Pd_2(dba)_3{\cdot}CHCl_3$ and 24 h for $Pd(OAc)_2$ respectively. [c] Reaction time was 36 h. [d] Reaction time was 72 h. [e] Reaction time was 48 h. [f] The products (**3**) were purified by silica gel column chromatography.

Good to excellent yields of **3k**−**o** were achieved from the reaction of **2f** and **2g** with **1a**−**c** in the presence of 2.5 mol % $Pd(OAc)_2$ and 5 mol % dppb in 5 mL of benzene after 24 h at 100 °C under 300 psi CO (entries 15, 17, 18, 19, and 21).

Benzo[*e*]-1,3-oxazin-2,4-diones (**5**) were obtained by the reaction of *o*-iodophenols (**1**) with isocyanates (**4**) and carbon monoxide catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$ and dppb in THF, and the results are summarized in Table 5. A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0025 mmol) and dppb (0.005 mmol) was stirred under N_2 for 15 min, and then 1 mmol each of **1b** and **4a** and 1.5 mmol of K_2CO_3 were added to the resulting solution. After the mixture was stirred at 80 °C under 300 psi CO for 12 h, complete

Table 5. Cyclocarbonylation of *o*-Iodophenols (1) with Isocyanates (4) Using $Pd_2(dba)_3$·$CHCl_3$-dppb[a]



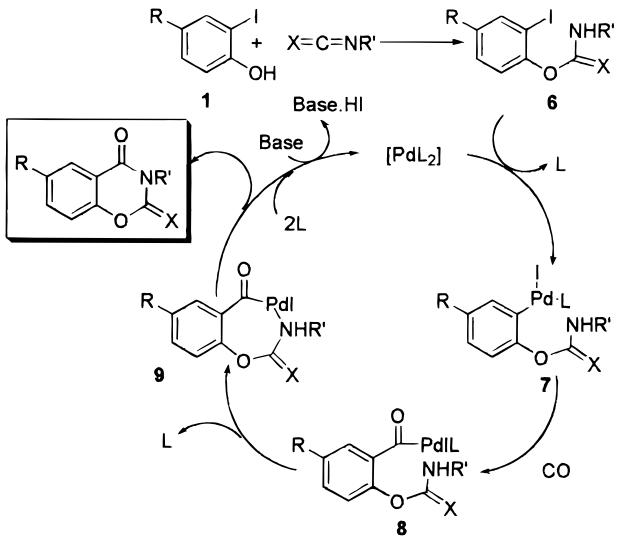
entry	1	O=C=NR′, 4	product	ratio of 1:4	isolated yield of 5[b] (%)
1	**1a**	O=C=NC_6H_4Cl-*p*, **4a**	**5a**	1:2	79
2	**1b**	**4a**	**5b**	1:2	84
3	**1b**	**4a**	**5b**	1:1	4
4	**1b**	O=C=NC_6H_4Br-*p*, **4b**	**5c**	1:2	77
5	**1c**	**4b**	**5d**	1:2	58
6	**1c**	**4b**	**5d**	1:1	0
7	**1a**	O=C=N$C_6H_4CH_3$-*p*, **4c**	**5e**	1:2	81
8	**1c**	**4c**	**5f**	1:2	52
9	**1c**	**4c**	**5f**	1:1	0
10	**1b**	O=C=N$C_6H_4OCH_3$-*p*, **4d**	**5g**	1:2	82
11	**1a**	O=C=N$CH_2C_6H_5$, **4e**	**5h**	1:2	79[c]

[a] Reaction conditions: **1**/**4**/K_2CO_3/$Pd_2(dba)_3$·$CHCl_3$/dppb 1:2:1.5: 0.0025:0.005 mmol in 5 mL of THF, 80 °C, 300 psi CO, 12 h. [b] Isolated by silica gel column chromatography. [c] 0.005 mmol $Pd(OAc)_2$ was used instead of $Pd_2(dba)_3$·$CHCl_3$.

conversion of isocyanate was observed and afforded **5b** but in only 4% yield (entry 3, Table 5). Performing the reaction under the same conditions but at a 2:1 ratio of **4a**/**1b** gave **5b** in 84% yield. No reaction occurred when a 1:1 ratio of **4**/**1** was used as in the case of **4b** (entry 6) and **4c** (entry 9); however, **5d** and **5f** were isolated in 52−58% yield by doubling the amount of the reactant isocyanates (entries 5 and 8). Those reactions that afford lower product yields may be a result of the presence of base in the reaction, which induces dimer or trimer formation of the isocyanates.[9] Good yields of benzo[*e*]-1,3-oxazin-2,4-diones (**5**) were attained by using **1**/**4**/K_2CO_3 in a ratio of 1:2:1.5 in the presence of 0.25 mol % of $Pd_2(dba)_3$·$CHCl_3$ and 0.5 mol % of dppb in THF under 300 psi CO at 80 °C for 12 h. An important application of this reaction is for the synthesis of 3-(benzyl)benzo-[*e*]-1,3-oxazin-2,4-dione (**5h**, entry 11), which may be effective against serine proteases. Note that $Pd(OAc)_2$−dppb was used instead of $Pd_2(dba)_3$·$CHCl_3$−dppb in order to obtain **5h** in better yield.[10]

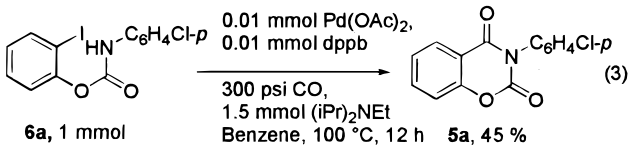
The mechanism of this reaction can be explained by the pathway outlined in Scheme 4. First the carbamate (**6**) may be formed in situ by reaction between *o*-iodophenols (**1**) with heterocumulenes. The latter undergo oxidative addition to $[PdL_2]$[11] and carbonyl insertion, affording aroylpalladium intermediates (**8**). Coordination of the amine moiety to aroylpalladium halide[12] to form intermediate **9** followed by HI neutralization, and reductive elimination would result in the formation of benzo[*e*]-1,3-oxazin-4-one derivatives. It is conceivable that intramolecular coupling occurs between the nitrogen

Scheme 4. Proposed Mechanism for the Cyclocarbonylation of *o*-Iodophenols with Heterocumulenes via an Aroylpalladium Intermediate



and the arylpalladium iodide moiety of **7**, followed by CO insertion to give **9**.

To prove that the carbamate ester was formed first before entering the catalytic cycle, **6a** was synthesized from the reaction of *o*-iodophenol (**1a**) with *p*-chlorophenylisocyanate (**4a**) in benzene. The resulting carbamate (1 mmol) was then used in the carbonylation reaction using 0.01 mmol $Pd(OAc)_2$, 0.01 mmol dppb, and 1.5 mmol (*i*-Pr)$_2$NEt in benzene under 300 psi CO (eq 3). After 12 h at 100 °C, complete conversion of the carbamate was detected by TLC and 45% of **5a** was isolated. Performing the reaction in a similar manner but adding an extra 1 mmol of **4a** to the reaction mixture resulted in the formation of 68% of **4a**.[13] This result also shows the importance of using excess isocyanate in palladium-catalyzed cyclocarbonylation with *o*-iodophenols in which the equilibrium for the formation of the corresponding carbamate ester was driven in such a manner as to give more **6**, which enters the catalytic cycle.



(3)

The cycloaddition reaction was also applied to unsymmetrical carbodiimides, and the results are listed in Table 6. We first used *N*-*n*-butyl-*N*′-phenylcarbodiimide (**10a**, 1 mmol) for the reaction with **1a** (1 mmol) in the presence of 0.0025 mmol of $Pd_2(dba)_3$·$CHCl_3$, dppb (0.005 mmol), and 1.5 mmol of K_2CO_3 in THF (5 mL). The reaction was stirred under 300 psi CO at 100 °C for 48 h. After

(9) Dimerization and trimerization of isocyanates were observed in the presence of base for the reaction at elevated temperature. See: Hofmann, A. W. *Ber.* **1860**, *3*, 761. Snape, H. L. *J. Chem. Soc.* **1886**, *49*, 254. Hofmann, A. W. *Ber.* **1885**, *18*, 764.

(10) When the reaction of **1a** with **4e** was performed by using the $Pd_2(dba)_3$·$CHCl_3$−dppb catalyst system, **5h** was obtained in a small amount with byproducts.

(11) For the mechanism of oxidative addition of aryl halides to palladium complexes; see: Stille, J. K.; Lau, K.S. Y. *Acc. Chem. Res.* **1976**, *10*, 434.

(12) Inter- and intramolecular coordination of amine to palladium aryl halide complexes was shown to enhance the acidity of the NH bond. See: (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *197*, 88232. (c) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794.

(13) **5a** was obtained in 65% isolated yield when 1 mmol of **1a** and 2 mmol of **4a**. A 1.5 mmol portion of (*i*-Pr)$_2$NEt was reacted in the presence of 1 mol % $Pd(OAc)_2$ and 1 mol % dppb under 300 psi CO in benzene at 100 °C for 12 h.

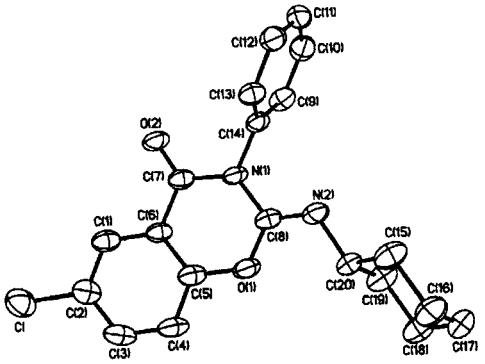
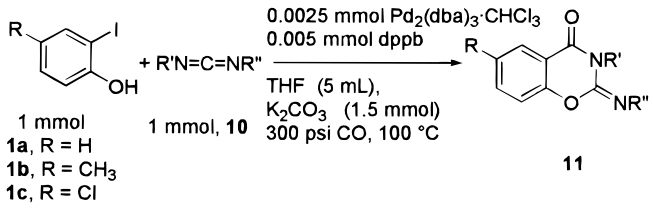


Figure 2. X-ray structure of **11d.**

Table 6. Cyclocarbonylation of *o*-Iodophenols (1) with Unsymmetrical Carbodiimides (10) Catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$ and dppb in THF[a]

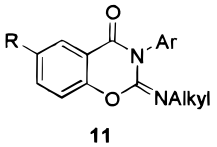


entry	**1**	R′=C=NR″, **10**	product	isolated yield of **11**[b] (%)
1	**1a**	$C_6H_5N{=}C{=}NC_4H_9$, **10a**	**11a**	94
2	**1c**	**10a**	**11b**	77
3	**1b**	$C_6H_5N{=}C{=}NC_6H_{11}$, **10b**	**11c**	94
4	**1c**	**10b**	**11d**	92
5	**1a**	p-$FC_6H_4N{=}C{=}NC_6H_{11}$, **10c**	**11e**	82
6	**1b**	**10c**	**11f**	82
7	**1a**	$2,6(CH_3)_2C_6H_3N{=}C{=}NC_4H_9$, **10d**	**11g**	93

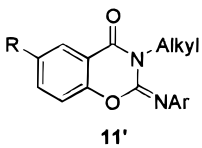
[a] Reaction conditions: **1** (1 mmol), **10** (1 mmol), K_2CO_3 (1.5 mmol), THF (5 mL), CO (300 psi), 100 °C, 48 h. [b] Isolated yield by silica gel chromatography.

purification of the solution, only one regioisomer was obtained in 94% yield (entry 1). Complete regioselectivity also resulted using either *o*-iodophenols or carbodiimides containing a substituent on the phenyl ring as reactants. For instance, only **11b** was formed using **1c** in reaction with **10a** (entry 2). Reaction of **1a**−**c** with **10b**−**d** gave only one isomer in high isolated yields (entries 3−7).

Two isomers are possible from reactions involving unsymmetrical carbodiimides, one with an aromatic substituent on the nitrogen of the oxazine ring (**11**) and the other with an alkyl group attached to the oxazine nitrogen (**11′**).



11

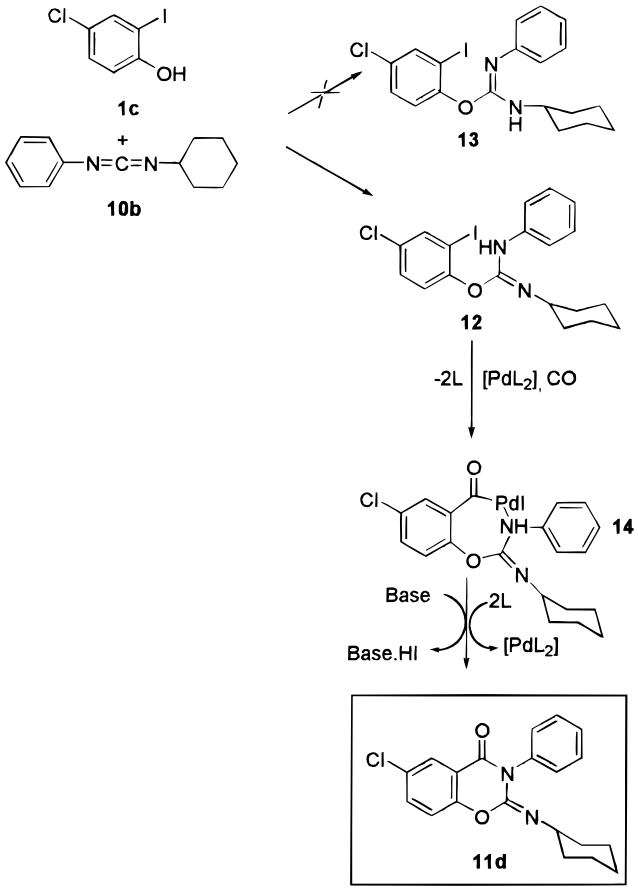


11'

To prove the structure of the products, an X-ray determination of **11d** was performed. The ORTEP diagram shows that **11d** contains a phenyl group on the nitrogen of the oxazine ring (Figure 2), which contrasts with the major (not exclusive) isomer resulting from the reaction of the same carbodiimide with vinyloxirane.[5b]

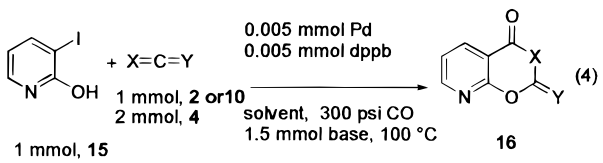
Only one isomer was obtained from the cyclocarbonylation of *o*-iodophenol (**1**) with unsymmetrical carbodiimides (**10a**−**d**). The selectivity may be due to the ease

Scheme 5. Proposed Mechanism for the Regioselective Formation of 11d



of formation of **12** compared to **13**. Reductive elimination of intermediate **14** and HI neutralization would furnish **11d** (Scheme 5).

When 3-iodo-2-hydroxypyridine (**15**) was employed for the cyclocarbonylation with carbodiimides in the presence of a catalytic amount of a palladium−dppb complex (eq 4), pyrido[3,2-*e*]-1,3-oxazin-4-ones were obtained in good yields (see Table 7).



$Pd(OAc)_2$ (entries 1 and 3) is superior to $Pd_2(dba)_3{\cdot}CHCl_3$ (entries 2 and 4) for the reaction of 3-iodo-2-hydroxypyridine (**15**) with heterocumulenes to form **16**. A mixture of regioisomers of **16c**, in a ratio of 2:1, resulted from the reaction using unsymmetrical carbodiimides (**10e**) (entry 5). No product was obtained in the reaction of **15** with *p*-chlorophenylisocyanate (**4a**), perhaps because the pyridine acts as reagent in the dimer formation of isocyanate.[14]

In conclusion, a novel method has been developed for the synthesis of benzo[*e*]-1,3-oxazin-4-ones and derivatives by the cyclocarbonylation of *o*-iodophenols with

(14) The dimerization of isocyanates catalyzed by pyridine and its derivatives was described by: Wiley, P. F. *J. Am. Chem. Soc.* **1949**, *71*, 3746.

Table 7. Cyclocarbonylation of 3-Iodo-2-hydroxypyridine (15) with Heterocumulenes (2a−b, 4a, 10e) Catalyzed by a Palladium Complex and dppb under 300 psi CO[a]

entry	X=C=Y	product	catalyst	isolated yield (%)
1	*p*-ClC_6H_4N=C=NC_6H_4Cl-*p*, **2a**	**16a**	$Pd(OAc)_2$	64[b]
2			$Pd_2(dba)_3$·$CHCl_3$	60[c]
3	*p*-$CH_3C_6H_4N$=C=$NC_6H_4CH_3$-*p*, **2b**	**16b**	$Pd(OAc)_2$	50[b,c]
4			$Pd_2(dba)_3$·$CHCl_3$	30[c]
5	*p*-ClC_6H_4N=C=NC_4H_9, **10e**	**16c** and **16′c**	$Pd(OAc)_2$	65 (2:1)[e]
6	*p*-ClC_6H_4N=C=O, **4a**	nd[f]	$Pd(OAc)_2$	0

[a] Reaction Conditions: **15** (1 mmol), **2** or **10** (1 mmol), 1.5 mmol of base [K_2CO_3 for $Pd_2(dba)_3$·$CHCl_3$, (*i*-Pr)$_2$NEt for $Pd(OAc)_2$], 0.005 mmol of Pd, 0.005 mmol of dppb, 300 psi CO, in 5 mL of solvent [THF for $Pd_2(dba)_3$·$CHCl_3$, benzene for $Pd(OAc)_2$] at 100 °C. [b] Reaction time was 24 h. [c] Reaction time was 48 h. [d] Isolated yield of **16b** after complete conversion of 15 after 24 h. [e] The ratio of **16c**:**16′c** was determined by GC. [f] The ratio of **15**:**4a** was 1:2 and complete conversion of the isocyanate occurred after 12 h at 80 °C; however, no desired produce was isolated.

heterocumulenes using a palladium complex and a bidentate phosphine. The yields are good to excellent, and the reaction proceeds with complete regioselectivity. Of particular note is the application of this reaction to the facile synthesis of a relative of a serine protease inhibitor.

Experimental Section

General Methods. $Pd(OAc)_2$, phosphine ligands, 2-iodophenol (**1a**), dicyclohexylcarbodiimide (**2f**), diisopropylcarbodiimide (**2g**), isocyanates (**4**), and 3-iodo-2-ohydroxypyridine (**15**) were purchased from commercial sources and were used as received. Carbodiimides (**2a**−**e**),[15] unsymmetrical carbodiimides[16] (**10a**−**e**), 4-methyl-2-iodophenol[17] (**1b**), 4-chloro-2-iodophenol[17] (**1c**), and $Pd_2(dba)_3$·$CHCl_3$[18] were prepared according to literature procedures. Organic solvents were dried and distilled prior to use.

General Procedure for the Palladium-Catalyzed Cyclocarbonylation of *o*-Iodophenols (1) with Carbodiimides (2a−g, 10a−d). An autoclave, its glass liner, and a magnetic stirring bar were dried in an oven and then cooled in a desiccator before use. The liner was charged with the palladium catalyst 0.5 mol % (unless otherwise noted in each case), 1 equiv of bidentate phosphine ligand relative to palladium was used, and 3 mL of dried solvent (THF for $Pd_2(dba)_3$·$CHCl_3$ or benzene for $Pd(OAc)_2$) was added. After the mixture was stirred under nitrogen for 15 min, *o*-iodophenol (**1**, 1 mmol), carbodiimide (**2** or **10**, 1 mmol), 1.5 mmol of base [K_2CO_3 for $Pd_2(dba)_3$·$CHCl_3$ or (*i*-Pr)$_2$NEt for $Pd(OAc)_2$], and another 2 mL of solvent was added to the mixture. The autoclave was then flushed three times with CO and pressurized to 300 psi. After 24 or 48 h [48 h for $Pd_2(dba)_3$·$CHCl_3$, 24 h for $Pd(OAc)_2$, unless otherwise stated] in an oil bath at 100 °C, the autoclave was removed from the oil bath and allowed to cool to room temperature. The excess gas was discharged and the system disassembled. The reaction mixture was filtered, and the filtrate was concentrated and purified by column chromatography on silica gel (1:1 ether/*n*-pentane). Melting points, IR, NMR, MS, and analytical data for selected samples of **3** and **11** are as follows (see the Supporting Information for all other data for **3** and **11**).

***N*-*p*-Chlorophenyl-3-*p*-chlorophenylbenzo[*e*]-1,3-oxazin-2-imin-4-one (3a)** (R = H, R′= *p*-ClC_6H_4): mp = 161−162 °C; IR (C=N) 1669, (C=O) 1710 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 6.90−8.12 (m, 12H); ^{13}C ($CDCl_3$, 75 MHz) δ 114.57, 115.76, 124.02, 124.95, 128.32, 128.66, 128.86, 129.72, 129.91, 134.26, 134.65, 136.02, 142.23, 142.91, 152.78, 159.50; MS *m*/*e* 382 $[M]^+$. Anal. Calcd for $C_{20}H_{12}Cl_2N_2O_2$: C, 62.68; H, 3.16; N, 7.31. Found: C, 62.82; H, 3.29; N, 7.26.

***N*-*p*-Chlorophenyl-3-*p*-chlorophenylbenzo[*e*]-6-methyl-1,3-oxazin-2-imin-4-one (3b)** (R = CH_3, R′= *p*-ClC_6H_4): mp = 164−165 °C; IR (C=N) 1671, (C=O) 1715 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H), 6.82−7.79 (m, 11H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.66, 114.19, 115.52, 124.08, 127.94, 128.64, 128.81, 129.71, 129.95, 134.40, 134.62, 134.94, 136.90, 142.71, 143.03, 150.91, 159.68; MS *m*/*e* 396 $[M-1]^+$, 397 $[M]^+$. Anal. Calcd for $C_{21}H_{14}Cl_2N_2O_2$: C, 63.49; H, 3.55; N, 7.05. Found: C, 63.28; H, 3.45;, N, 6.95.

***N*-*n*-Butyl-3-phenylbenzo[*e*]-1,3-oxazin-2-imine-4-one (11a)** (R = H, R′ = C_6H_5, R″ = C_4H_9): mp = 107−108 °C; IR (C=N) 1652, (C=O) 1711 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 1.12 (d, 6H *J* = 6.33 Hz), 1.47 (d, 6H, *J* = 6.92 Hz), 4.03 (Sept, 1H, *J* = 6.3 Hz), 5.20 (Sept, 1H, *J* = 6.9 Hz) 6.99 (m, 1H), 7.43 (m, 1H), 7.88 (m,1H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.59, 19.77, 31.68, 41.20, 119.79, 123.20, 124.38, 126.25, 128.97, 130.04, 131.85, 138.03, 147.68, 154.76, 164.15; MS *m*/*e* 293 $[M-1]^+$, 294 $[M]^+$; Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.20; H, 5.98; N, 9.11.

***N*-*n*-Butyl-3-phenylbenzo[*e*]-6-chloro-1,3-oxazin-2-imin-4-one (11b)** (R = Cl, R′ = C_6H_5, R″ = C_4H_9): mp = 126−127 °C; IR (C=N) 1672, (C=O) 1714 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 0.86 (t, 3H), 1.18−1.62 (m, 4H), 3.362. (dd, 2H, *J* = 6.96 and 6.86 Hz), 7.11−8.00 (m, 8H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.88, 20.44, 32.64, 45.50, 116.16, 117.03, 127.79, 128.43, 128.51, 129.29, 129.60, 135.37, 136.13, 141.49, 151.75, 159.84; MS *m*/*e* 327 $[M-1]^+$, 328 $[M]^+$. Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52. Found: C, 65.74; H, 5.04; N, 8.50.

General Procedure for the Palladium-Catalyzed Cyclocarbonylation of *o*-Iodophenols (1) with Isocyanates 4a−e. The cyclocarbonylation reactions of *o*-iodophenols with isocyanates were performed in a manner similar to that with carbodiimides but 2 equiv of isocyanate was used in order to obtain higher product yield. The reaction mixtures were stirred in an oil bath at 80 °C for 12 h. After filtration and rotary evaporation of the filtrate, the residue was purified by silica gel column chromatography (using 1:1, ethyl acetate/*n*-pentane as eluant). Melting points, IR, NMR, MS, and analytical data for selected example **5** are as follows (see the Supporting Information for all other data for **5**).

3-(*p*-Chlorophenyl)benzo[*e*]-1,3-oxazin-2,4-dione (5a) (R = H, R′ = *p*-ClC_6H_4): mp = 236−238 °C; IR (C=O) 1705, 1770 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 7.20−8.12 (m, 8H); ^{13}C ($CDCl_3$, 75 MHz) δ 114.15, 116.66, 125.76, 128.48, 129.49, 129.87, 132.53, 136.68, 152.69, 160.48; MS *m*/*e* 273 $[M]^+$. Anal. Calcd for $C_{14}H_8ClNO_3$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.60; H, 4.73; N, 8.49.

3-(*p*-Chlorophenyl)benzo[*e*]-6-methyl-1,3-oxazine-2,4-diones (5b) (R = CH_3, R′ = *p*-ClC_6H_4): mp = 190−191 °C; IR (C=O) 1704, 1759 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H), 7.21−7.88 (m, 7H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.71, 113.75, 116.39, 127.95, 129.51, 129.82, 132.67, 135.30, 135.83, 137.59, 147.86, 150.78, 160.61; MS *m*/*e* 287 $[M]^+$. Anal. Calcd for $C_{15}H_{10}ClNO_3$: C, 62.62; H, 3.50; N, 4.87. Found: C, 62.45; H, 3.40; N, 4.80.

General Procedure for the Palladium-Catalyzed Cyclocarbonylation of 3-Iodo-2-hydroxypyridine (15) with Heterocumulenes. The cyclocarbonylation reactions of 3-iodo-2-hydroxypyridine with heterocumulenes (**2a**,**b**, **4a**, **10e**) were performed following the same procedure as that used for the

(15) Campbell, T. W.; Monagle, J. J. Foldi, V. *J. Am. Chem. Soc.* **1962**, *84*, 3673.
(16) Palomo, C.; Mestres, R. *Synthesis* **1981**, 373.
(17) Dains, F. B.; Eberly, F. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. 2, p 355.
(18) Ukai, T.; Kawazura, H.; Ishii, Y. *J. Organomet. Chem.* **1974**, *65*, 253.

reaction of *o*-iodophenols with carbodiimides and isocyanates. Melting points, IR, NMR, MS, and analytical data of **16** after purification by silica gel column chromatography are shown below.

***N*-*p*-Chlorophenyl-3-*p*-chlorophenylpyrido[3,2-*e*]-1,3-oxazin-2-imin-4-one (16a)** (X = Y = *p*-ClC_6H_4N): mp = 221−223 °C; IR (C=N) 1674, (C=O) 1728 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 6.86 (m, 2H), 7.24−7.61 (m, 8H), 8.66 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 123.81, 124.41, 128.73, 129.18, 129.64, 129.79, 131.98, 133.99, 134.85, 141.21, 142.40, 147.49, 150.63, 157.94; MS *m*/*e* 383 $[M - 1]^+$, 384 $[M]^+$. Anal. Calcd for $C_{19}H_{11}Cl_2N_3O_2$: C, 59.39; H, 2.89; N, 10.94. Found: C, 59.04; H, 2.88; N, 10.88.

***N*-*p*-Tolyl-3-*p*-tolylpyrido[3,2-*e*]-1,3-oxazin-2-imin-4-one (16b)** (X = Y = *p*-$CH_3C_6H_4N$): mp = 233−235 °C; IR (C=N) 1671, (C=O) 1713 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.29 (s, 3H), 2.40 (s, 3H), 6.84−7.52 (m, 10H), 8.65 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.82, 21.25, 122.30, 124.29, 128.00, 129.14, 129.26, 130.15, 132.32, 133.14, 138.66, 140.83, 141.46, 147.08, 150.70, 158.31; MS *m*/*e* 342 $[M-1]^+$, 343 $[M]^+$. Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99;, N, 12.24. Found: C, 73.56; H, 5.07; N, 12.07.

***N*-*n*-Butyl-3-*p*-chlorophenylpyrido[3,2-*e*]-1,3-oxazin-2-imin-4-one (16c)** (X = *p*-ClC_6H_4N, Y = C_4H_9N): mp = 157−159 °C; IR (C=N) 1681, (C=O) 1717 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 0.86 (t, 3H), 1.23−1.47 (m, 4H), 3.37 (t, 3H), 7.21 (m, 2H), 7.41 (m, 2H), 7.56 (m, 2H), 8.63 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.83, 20.41, 32.58, 45.54, 124.04, 129.31, 129.58, 129.87, 132.25, 134.38, 134.54, 140.62, 146.83, 150.89, 158.25; MS *m*/*e* 328 $[M - 1]^+$, 329 $[M]^+$. Anal. Calcd for $C_{17}H_{16}ClN_3O_2$: C, 61.91; H, 4.89; N, 12.74. Found: C, 62.04; H, 5.07; N, 12.48.

***N*-*p*-Chlorophenyl-3-*n*-butylpyrido[3,2-*e*]-1,3-oxazin-2-imin-4-one (16c′)** (X = C_4H_9N, Y = *p*-ClC_6H_4N): mp = 118−120 °C; IR (C=N) 1665, (C=O) 1719 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 0.93 (t, 3H) 1.41 (m,2H), 1.75 (m, 2H), 4.21 (t, 2H), 6.97 (m, 2H), 7.29 (m, 2H), 7.49 (m, 2H), 8.62 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.83, 20.09, 28.98, 43.46, 123.99, 124.11, 128.87, 129.10, 132.06, 140.45, 146.02, 147.26, 150.26, 157.94; MS *m*/*e* 328 $[M - 1]^+$, 329 $[M]^+$; HRMS calcd for $C_{17}H_{16}ClN_3O_2$ 329.0931, found 329.0907.

Preparation of Carbamate Ester 6a. In a 50-mL round-bottom flask equipped with a stirring bar was added dropwise *o*-iodophenol **1a** (1 g, 4.5 mmol) in benzene (5 mL) to a 10 mL solution of 0.7 g (4.5 mmol) of *p*-chlorophenylisocyanate **4a**. After the mixture was stirred at room temperature under N_2 overnight, the resulting solution was concentrated and purified by silica gel column chromatography. Carbamate ester **6a** was obtained (1.22 g, 71%).

Carbamate **6a**: mp = 123−125 °C; IR (C=O) 1727 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 6.97 (m, 1H), 7.35 (m, 7H), 7.80 (dd, 1H, J = 7.9 and 1.4 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 90.68, 120.05, 123.28, 127.73, 129.13, 129.48, 135.73, 139.37, 150.47; MS *m*/*e* 373 $[M]^+$; HRMS calcd for $C_{13}H_9ClINO_2$ 372.9367, found 372.9353.

Palladium Catalyzed Cyclocarbonylation of Carbamate 6a. To a 45-mL Parr autoclave fitted with a glass liner and a stirring bar were added $Pd(OAc)_2$ (0.01 mmol), dppb (0.01 mmol), **6a** (1 mmol), *N*,*N*-diisopropylethylamine (1.5 mmol), and dried benzene (5 mL). The autoclave was fill-vented three times with CO and pressurized to 300 psi CO. The reaction mixture was stirred at 100 °C for 12 h. The excess CO was released, and the resulting reaction mixture was separated by silica gel column chromatography, affording **5a** in 45% isolated yield. Performing the same reaction but in the added presence of **4a** (1 mmol) afforded **5a** in 68% yield.

Single-Crystal Diffraction Study of 11d. Suitable crystals of **11d** were selected and mounted on thin glass fibers using epoxy cement. Data were collected on a Bruker AX SMART 1k CCD diffractometer using 0.3° ω-scans at 0, 90, and 180° in ϕ. Unit-cell parameters were determined from 60 data frames collected at different sections of the Ewald sphere. No absorption corrections were required (μ_{eff} = 2.24 cm^{-1}).

Systematic absences in the diffraction data and unit-cell parameters were uniquely consistent with the reported space group. The structure was solved by direct methods, completed with difference Fourier syntheses, and refined with full-matrix least-squares procedures based on F^2. The Flack parameter refined to nil, indicating that the true hand of the data has been determined correctly. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were treated as idealized contributions. All scattering factors and anomalous dispersion factors are contained in the SHEXTL 5.03 program library (Sheldrick, 1997, WI).

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Supporting Information Available: Spectral data of compounds **3c**−**o**, **5c**−**h**, and **11**−**11g**; ^1H and ^{13}C NMR spectra of compounds **3n**, **6a**, **11g**, **16′c**; text giving full details of the X-ray structure of **11d** including the experimental procedures, tables of crystal data, structure refinements, atomic coordination parameters, bond lengths, bond angles, anisotropic displacement parameters, and hydrogen coordination parameters. This material is available free of charge via the Internet at http:/pubs.acs.org.

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