Expedient Synthesis of 4-Dialkylamino-5*H*-furan-2-ones by One-Pot Sequential Pd-Catalyzed Oxidative Carbonylation of 2-Yn-1-ols – Conjugate Addition-Lactonization

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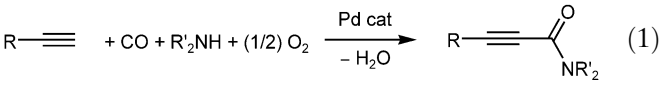
Received: September 29, 2003; Accepted: December 7, 2003

Abstract: A novel synthesis of 4-dialkylamino-5*H*-furan-2-ones **3** starting from very simple building blocks, i.e., α-substituted 2-yn-1-ols **1**, carbon monoxide, dialkylamines **2** and oxygen is reported. Reactions are carried out in 1,2-dimethoxyethane at 100 °C and under 20 atm (at 25 °C) of a 4/1 mixture of CO/air in the presence of catalytic amounts of PdI_2 in conjunction with 10 equiv. of KI. Formation of **3** occurs through an ordered sequence of steps, namely (a) Pd-catalyzed oxidative monoaminocarbonylation of **1** to give 4-hydroxy-2-ynamides **4**, which can be isolated under appropriate conditions; (b) stereoselective conjugate addition of **2** to the triple bond of **4**, with formation of (not isolated) (*E*)-3-dialkylamino-4-hydroxy-2-enamides; (c) intramolecular alcoholysis of the amide function of the latter to give the final product **3**.

Keywords: aminocarbonylation; 4-amino-5*H*-furan-2-ones; carbonylation; cyclization; palladium; 2-yn-1-ols

Introduction

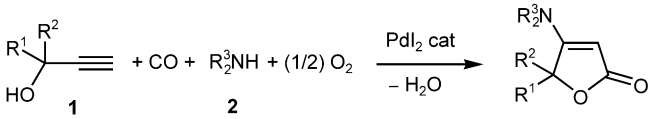
We recently reported the first example of catalytic monoaminocarbonylation of terminal alkynes with formation of 2-ynamides in good yields according to Eq. (1).[1]



(1)

Reactions were carried out using a secondary dialkylamine as nucleophile (alkyne/amine molar ratio = 1:1) in dioxane at 100 °C under 20 atm of a 4/1 mixture of CO/air and were catalyzed by PdI_2 (0.2 mol %) in conjunction with KI (10 equiv. with respect to PdI_2). The selective formation of 2-ynamides, rather than of maleic or fumaric derivatives obtained using alcohols or water as nucleophiles under analogous conditions,[2] was due to the basicity of the amines, which promoted the preferential formation of an alkynylpalladium complex **I** from the terminal alkyne and PdI_2 (Scheme 1; in this and in the following Schemes anionic iodide ligands are omitted for clarity). Carbon monoxide insertion followed by nucleophilic displacement by the amine led to the final product and Pd(0), readily reoxidized by oxidative addition of I_2, generated in turn by oxidation of HI by oxygen.

We now report a useful application of this methodology, which allows a direct, one-pot preparation of 4-dialkylamino-5*H*-furan-2-ones **3** starting from very simple building blocks, i.e., 2-yn-1-ols **1**, carbon monoxide, dialkylamines **2**, and oxygen, Eq. (2).

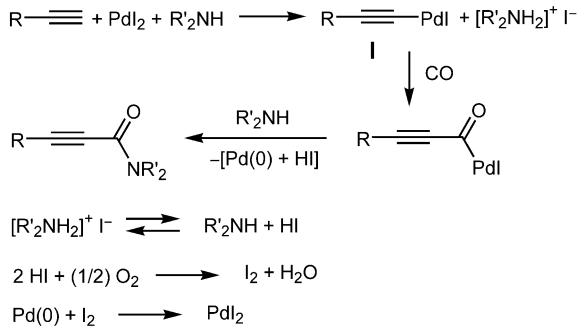


aa $R^1 = R^2 = Me$, R^3_2NH = morpholine: 85%
ba $R^1 = Et$, $R^2 = Me$, R^3_2NH = morpholine: 78%
ca R^1-R^2 = cyclohexyl, R^3_2NH = morpholine: 80%
da $R^1 = Et$, $R^2 = H$, R^3_2NH = morpholine: 82%
ea $R^1 = (CH_2)_2Ph$, $R^2 = H$, R^3_2NH = morpholine: 81%
ab $R^1 = R^2 = Me$, R^3_2NH = piperidine: 80%
eb $R^1 = (CH_2)_2Ph$, $R^2 = H$, R^3_2NH = piperidine: 78%
ac $R^1 = R^2 = Me$, $R^3 = Et$: 60%
bc $R^1 = Et$, $R^2 = Me$, $R^3 = Et$: 58%
cc R^1-R^2 = cyclohexyl, $R^3 = Et$: 57%
dc $R^1 = R^3 = Et$, $R^2 = H$: 60%
ec $R^1 = (CH_2)_2Ph$, $R^2 = H$, $R^3 = Et$: 65%
fa R^1 = mesityl, $R^2 = H$: 61%

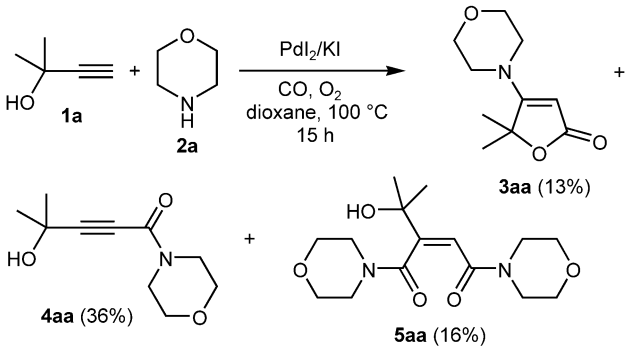
(2)

We have in fact found that, under suitable conditions, 2-yn-1-ols **1** undergo an ordered sequence of processes, involving (a) Pd-catalyzed oxidative monoaminocarbonylation of the triple bond of **1** with retention of the

 DOI: 10.1002/adsc.200303151



Scheme 1.



(3)

hydroxy group leading to 4-hydroxy-2-ynamides **4**; (b) stereoselective conjugate addition of **2** to the triple bond of **4**, with formation of (*E*)-3-dialkylamino-4-hydroxy-2-enamides; (c) intramolecular alcoholysis of the amide function of the latter to give furanones **3** (Scheme 2).

This reaction represents the first example reported in the literature of a one-pot sequential oxidative carbonylation – conjugate addition – lactonization reaction.[3] To our knowledge, the present reaction is also the first example of synthesis of 4-aminofuran-2-one derivatives by a carbonylation approach.[4–6] 4-Aminofuranones are very interesting heterocyclic derivatives, since they are useful precursors for the preparation of tetronic acids,[7] whose biological activity is well-known;[8] moreover, several molecules incorporating the 4-amino-5*H*-furan-2-one core have shown interesting pharmacological activity.[9]

Results and Discussion

2-Methylbut-3-yn-2-ol **1a** and morpholine **2a** were first used as substrates. The reaction between **1a** and **2a** was initially carried out under conditions similar to those employed for the aminocarbonylation of 1-alkynes,[1] i.e., with PdI_2 in conjunction with KI as catalyst (PdI_2/KI/**1a**/**2a** molar ratio = 1:10:100:100) at 100 °C and under 16 atm of CO and 4 atm of air (20 atm total at 25 °C) in dioxane as the solvent (concentration of **1a** = 0.5 mmol/mL of dioxane). After 15 h, a mixture of 5,5-dimethyl-4-morpholin-4-yl-5*H*-furan-2-one **3aa** (13%), 4-hydroxy-4-methyl-1-morpholin-4-ylpent-2-ynone **4aa** (36%), and (*Z*)-2-(1-hydroxy-1-methylethyl)-1,4-dimorpholin-4-yl-but-2-ene-1,4-dione **5aa** (16%) was obtained at 100% substrate conversion [Eq. (3), and Table 1, entry 1].

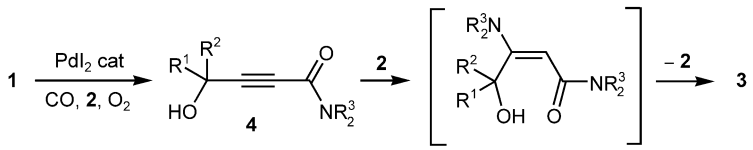
The structures of the products were established by spectroscopic techniques and, in the case of **3aa**, confirmed by single crystal X-ray diffraction analysis. Figure 1 shows the molecular structure of **3aa**, in which the flat furan-2-one ring is bonded through the nitrogen atom to the morpholine ring, found to be in a typical chair conformation.

4-Hydroxy-2-ynamide **4aa** corresponded to oxidative monoaminocarbonylation of the triple bond of **1a**, and its formation could be rationalized according to the same mechanistic pathway already proposed for simple 1-alkynes (Scheme 1), involving the formation of a β-hydroxyalkynylpalladium species as the key intermediate.

On the other hand, maleic bis-amide **5aa** was formed through a mechanism similar to that leading to maleic derivatives by PdI_2/KI-catalyzed oxidative dicarbonylation of simple 1-alkynes,[1–2] implicating the formation of an acylpalladium species **II** that undergoes nucleophilic displacement by the amine (Scheme 3).

Much more interesting, however, was the formation of aminofuranone **3aa**, which formally corresponded to an oxidative aminocyclocarbonylation process. On the grounds of our previous knowledge on the PdI_2/KI-catalyzed oxidative dialkoxycarbonylation of 2-yn-1-ols and 3-yn-1-ols,[10] a possible mechanism leading to **3aa** could start with the formation of alkoxycarbonylpalladium complex **III** from the reaction between the alcoholic function of **1a** with PdI_2 and CO, followed by nucleophilic attack by **2a** to the triple bond coordinated to palladium and reductive elimination of Pd(0) (Scheme 4).

Formation of **3aa** through the mechanism shown in Scheme 4, however, would implicate a selective attack of the amine on the internal carbon of the triple bond of



Scheme 2.

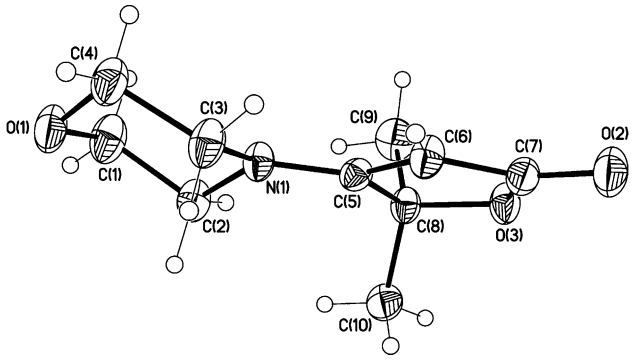


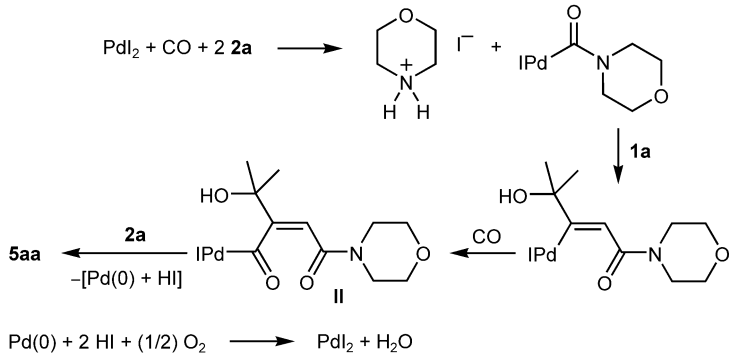
Figure 1. Molecular structure of 5,5-dimethyl-4-morpholin-4-yl-5*H*-furan-2-one **3aa** showing the atom labeling scheme and displacement ellipsoids at the 30% probability level.

III, which is not very likely. Alternatively, **3aa** could be formed from ynamide **4aa** through a subsequent stereoselective conjugate addition of **2a** to the triple bond of **4aa** followed by intramolecular alcoholysis (Scheme 5).

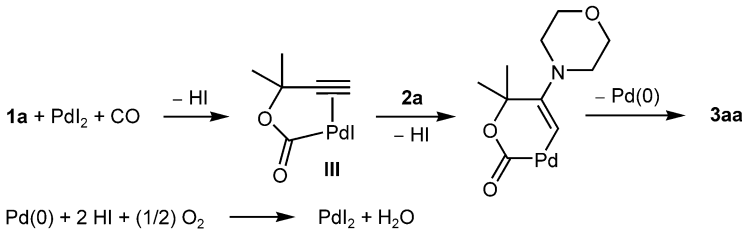
In order to test the likelihood of this latter mechanism, we carried out low-conversion experiments. After 3 h rather than 15 h reaction time, GLC analysis of the reaction mixture revealed the formation of ynamide **4aa** and furanone **3aa** in 26% and 1% yield, respectively, at 32% conversion of **1a** (entry 2). This result strongly suggests that **4aa** is actually the intermediate in the formation of furanone **3aa**, according to Scheme 5.

When the reaction was carried out with an excess of **2a** with respect to **1a**, conversion of **1a** was faster and a higher **3aa**/**4aa** ratio was obtained (entries 3–5). In particular, with a **2a**/**1a** molar ratio of 5, **1a** conversion reached 67% after 3 h, with a 23% yield of **3aa** and a 42% yield of **4aa** (entry 4, to be compared with entry 2) and was quantitative after 15 h, with yields in **3aa** and **4aa** of 82% and 6%, respectively (entry 5, to be compared with entry 1). These results are in agreement with the mechanisms shown in Schemes 1 and 5, since *both* the formation of alkynylpalladium complex **I** *and* conjugate addition of **2a** to **4aa** are clearly favored by the presence of a larger amount of the amine. In agreement with Scheme 5, working with a higher substrate concentration also resulted in an increase of the **3aa**/**4aa** ratio: under the same conditions of entry 4, but with a **1a** concentration of 1.0 rather than 0.5 mmol/mL of dioxane, furanone **3aa** was in fact the main reaction product (46% GLC yield, **4aa** being formed in 18% yield) at 71% conversion of **1a** (entry 6). Interestingly, a higher **3aa**/**4aa** ratio was also observed working in 1,2-dimethoxyethane (DME) as the solvent rather than dioxane, as it can be seen by comparing entry 7 with entry 4.

On the basis of the results obtained above, the next experiments, aimed at achieving efficiency (mol of carbonylated products per mol of catalyst) and selectivity towards **3aa**, were carried out using a **2a**/**1a** molar ratio of 5:1 in DME as the solvent with a concentration of **1a** of 1 mmol/mL of DME (entries 8–10). After 15 h, using 1 mol % of PdI_2 with respect to **1a**, **3aa** was obtained as the sole product in 88% GLC yield [85% isolated, entry 8 and Eq. (2)] at total **1a** conversion. With 0.3% of PdI_2, **1a** conversion was 100% after 24 h, again with selective formation of **3aa** (85% GLC yield, 78% isolated, entry 10). As a further confirmation of the



Scheme 3.

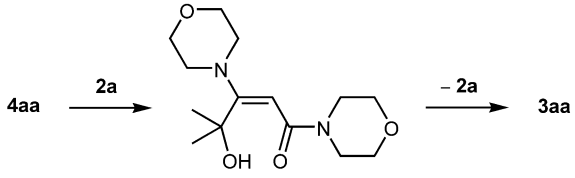


Scheme 4.

Table 1. Reactions of 2-methylbut-3-yn-2-ol **1a** with morpholine **2a**, CO and O_2 in the presence of PdI_2 and KI (KI/PdI_2 molar ratio = 10), $p(CO) = 16$ atm, $p(air) = 4$ atm, $T = 100\,^{\circ}C$.

Entry	**2a**/**1a**/PdI_2	Solvent	Concentration of **1a**[a]	t [h]	Conversion of **1a** [%][b]	Yield of **3aa** [%][c]	Yield of **4aa** [%][c]
1	100:100:1	Dioxane	0.5	15	100	(13)	(36)[d]
2	100:100:1	Dioxane	0.5	3	32	1	26
3	300:100:1	Dioxane	0.5	3	57	18	33
4	500:100:1	Dioxane	0.5	3	67	23	42
5	500:100:1	Dioxane	0.5	15	100	82 (75)	6
6	500:100:1	Dioxane	1.0	3	71	46	18
7	500:100:1	DME	0.5	3	79	35	44
8	500:100:1	DME	1.0	15	100	88 (85)	
9	1000:200:1	DME	1.0	15	98	83 (75)	traces
10	1500:300:1	DME	1.0	24	100	85 (78)	traces

[a] Mmol of **1a**/mL of solvent.
[b] Based on starting **1a**, by GLC.
[c] GLC yield (isolated yield) based on **1a**.
[d] The reaction also led to the formation of (*Z*)-2-(1-hydroxy-1-methylethyl)-1,4-dimorpholin-4-ylbut-2-ene-1,4-dione **5aa** (16% isolated yield).



Scheme 5.

mechanism shown in Scheme 5, we let pure **4aa** to react under the same conditions reported in entry 8 (with a **2a**/**4aa** molar ratio of 4), observing its quantitative conversion into **3aa**. The same result was also obtained working under nitrogen and in the absence of PdI_2/KI: this means that catalysis by palladium does not play a significant role in the conjugate addition of **2a** to **4aa**.

The reaction was successfully extended to other dialkylamines and different α-monoalkyl-substituted or α,α-dialkyl-substituted 2-yn-1-ols [Eq. (2) and Table 2, entries 11–25].[11] High yields in the corresponding aminofuranones **3** (76–90% by GLC, 70–82% isolated) were obtained when the reaction was carried out in the presence of secondary cyclic amines such as morpholine (entries 11–18) or piperidine (entries 19–20). The yields were slightly lower with dialkyl acyclic amines such as diethylamine (63–71% by GLC, 57–65% isolated, entries 21–25), while no reaction leading to **3** took place with primary amines, which, as we already reported,[12] underwent oxidative carbonylation to substituted ureas. The reaction of 1-phenylprop-2-yn-1-ol ($R^1 = Ph$, $R^2 = H$) with **2a** under the same conditions of entries 11–12 led to a mixture of products, in which the desired aminofuranone was present in low yield (not higher than 25% by GLC), and was not examined further. Quite interestingly, however, a sterically hindered α-arylpropynyl alcohol such as 1-(2,4,6-trimethylphenyl)prop-2-yn-1-ol **1f** afforded the desired aminofuranone **3fa** in satisfactory yield (66% by GLC, 61% isolated, entry 26).

Conclusion

In conclusion, we have reported the first example of a one-pot sequential oxidative carbonylation–conjugate addition–lactonization reaction, leading to important heterocyclic derivatives **3** starting from very simple building blocks, i.e., 2-yn-1-ols **1**, carbon monoxide, dialkylamines **2** and oxygen under mild conditions. The highly efficient introduction of only certain molecules in ordered sequence with selective formation of a multifunctionalized product is remarkable, also in view of other possible competitive pathways that could take place. For example, we have seen that maleic bis-amides **5**, formed through the mechanism shown in Scheme 3, were obtained (and still in small amounts) only when the reaction was carried out with an equimolecular amount of **1** and **2** under non-optimized conditions (entry 1). On the contrary, triple bond aminocarbonylation occurs selectively with preservation of the triple bond and of the OH group, followed by stereoselective amination, and this event causes the OH and $CONR_2$ moieties to arrange in a way to allow their reaction to give the final 4-aminofuranones **3**.

Experimental Section

General Remarks

Melting points were determined with a Reichert Thermovar melting point apparatus and are uncorrected. Elemental analyses were carried out with a Carlo Erba Elemental

Table 2. Synthesis of 4-dialkylamino-5*H*-furan-2-ones **3** by oxidative aminocarbonylation of propynyl alcohols **1**.[a]

Entry	**1**	R^1	R^2	**2**	$R^3{}_2NH$	**2**:**1**:PdI_2	*t* [h]	**3**	Yield of **3** [%][b]
11	**1b**	Et	Me	**2a**	Morpholine	1000:200:1	15	**3ba**	76 (70)
12	**1b**	Et	Me	**2a**	Morpholine	1500:300:1	24	**3ba**	86 (78)
13	**1c**	$(CH_2)_5$		**2a**	Morpholine	1000:200:1	15	**3ca**	78 (71)
14	**1c**	$(CH_2)_5$		**2a**	Morpholine	1500:300:1	24	**3ca**	87 (80)
15	**1d**	Et	H	**2a**	Morpholine	1000:200:1	15	**3da**	86 (81)
16	**1d**	Et	H	**2a**	Morpholine	1500:300:1	24	**3da**	90 (82)
17	**1e**	$(CH_2)_2Ph$	H	**2a**	Morpholine	1000:200:1	15	**3ea**	90 (81)
18	**1e**	$(CH_2)_2Ph$	H	**2a**	Morpholine	1500:300:1	24	**3ea**	89 (81)
19	**1a**	Me	Me	**2b**	Piperidine	1500:300:1	24	**3ab**	87 (80)
20	**1e**	$(CH_2)_2Ph$	H	**2b**	Piperidine	1500:300:1	24	**3eb**	85 (78)
21	**1a**	Me	Me	**2c**	Et_2NH	250:50:1	15	**3ac**	66 (60)
22	**1b**	Et	Me	**2c**	Et_2NH	250:50:1	15	**3bc**	64 (58)
23	**1c**	$(CH_2)_5$		**2c**	Et_2NH	250:50:1	15	**3cc**	63 (57)
24	**1d**	Et	H	**2c**	Et_2NH	250:50:1	15	**3dc**	67 (60)
25	**1e**	$(CH_2)_2Ph$	H	**2c**	Et_2NH	250:50:1	15	**3ec**	71 (65)
26	**1f**	mesityl	H	**2a**	Morpholine	1500:300:1	24	**3fa**	66 (61)

[a] All reactions were carried out in DME (1 mmol of **1**/mL of DME, 8–10 mmol scale based on **1**) at 100 °C under 20 atm (at 25 °C) of a 4/1 mixture of CO/air in the presence of PdI_2 in conjunction with 10 equiv. of KI.
[b] GLC yield (isolated yield) based on **1**. Substrate conversion was practically quantitative in all cases.

Analyzer Mod. 1106. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on a Bruker AC 300 spectrometer in $CDCl_3$ solutions at 300 MHz and 75 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with a Perkin-Elmer Paragon 1000 PC FT-IR spectrometer. Mass spectra were obtained using an HP 5972A GC-MS apparatus at 70 eV ionization voltage. 1,4-Dioxane and DME were dried over sodium and distilled over sodium under nitrogen before use. All reaction mixtures were analyzed by TLC on silica gel 60 F_{254} or by GLC using a Shimadzu GC-14A gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase (HP-5). Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh).

All substrates, with the exception of **1e**,[13] and **1f**[14] which were prepared according to literature procedures, were commercially available and were used without further purification.

Typical Procedure for Oxidative Carbonylation of 2-Methylbut-3-yn-2-ol 1a and Morpholine 2a (1:1 Molar Ratio) in Dioxane (Table 1, Entry 1) and Separation of Products

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (15.0 mg, 4.2×10^{-2} mmol), KI (69.9 mg, 4.2×10^{-1} mmol) and a solution of **1a** (351.2 mg, 4.2 mmol) and **2a** (365.4 mg, 4.2 mmol) in dioxane (8.4 mL). The autoclave was pressurized at room temperature with stirring with CO (16 atm) and air (up to 20 atm of total pressure), and then heated at 100 °C with stirring for 15 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the products purified by column chromatography using hexane/acetone, 6:4, as eluent; order of elution: **4aa** (299.1 mg, 36% based on **1a**), **3aa** (109.8 mg, 13% based on **1a**), **5aa** (207.4 mg, 16% based on **1a**).

Typical Procedure for Oxidative Carbonylation of 2-Yn-1-ols 1a–f with Amines 2a, b (1:5 Molar Ratio) in DME (Table 1, Entries 8–10 and Table 2, Entries 11–20 and Entry 26)

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (10.0 or 15.0 or 30.3 mg, 2.8×10^{-2} or 4.2×10^{-2} or 8.4×10^{-2} mmol), KI (46.0 or 69.0 or 140.0 mg, 2.8×10^{-1} or 4.2×10^{-1} or 4.2×10^{-1} mmol) and a solution of **1** (8.4 mmol) and **2** (42.0 mmol) in DME (8.4 mL). The autoclave was pressurized at room temperature with stirring with CO (16 atm) and air (up to 20 atm of total pressure), and then heated at 100 °C with stirring for 15–24 h (see Tables 1 and 2 for the **1**/PdI_2 molar ratio and the reaction time required for each substrate). After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and products **3** purified as described below.

Typical Procedure for Oxidative Carbonylation of 2-Yn-1-ols 1a–e with Diethylamine 2c (1:5 Molar Ratio) in DME (Table 2, Entries 21–25)

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (60.0 mg, 1.7×10^{-1} mmol), KI (282.0 mg, 1.7 mmol) and a solution of **1** (8.5 mmol) and **2c** (3.1 g, 42.4 mmol) in DME (8.5 mL). The autoclave was pressurized at room temperature with stirring with CO (16 atm) and air (up to 20 atm of total pressure), and then heated at 100 °C with stirring for 15 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and products **3** purified as described below.

Purification of Products 3

Products **3aa** and **3da** were purified by column chromatography using 6:4 hexane/acetone as eluent, followed by repeated crystallization through dissolution in the minimum amount of $CHCl_3$ followed by precipitation with hexane. Products **3ba**, **3ca** and **3ea** were purified by column chromatography using 7:3 hexane/acetone as eluent, followed by repeated crystallization through dissolution in the minimum amount of $CHCl_3$ followed by precipitation with hexane. Products **3ab**, **3eb**, **3ac**, **3bc**, **3cc**, **3dc** were purified by column chromatography using 7:3 hexane/acetone as eluent. Product **3ec** was purified by column chromatography using 6:4 hexane/acetone as eluent. Compound **3fa** was purified by column chromatography using 8:2 hexane/acetone as eluent.

5,5-Dimethyl-4-morpholin-4-yl-5*H*-furan-2-one (3aa): Yield: 1.41 g, starting from 707 mg of **1a** (85%, Table 1, entry 8). Colorless solid, mp 162–164 °C. IR (KBr): ν = 1732 (s), 1598 (s), 1317 (w), 1276 (m), 1233 (m), 1114 (m), 982 (m), 912 (m), 879 (w) cm^{-1}; ^1H NMR: δ = 1.61 (s, 6H, 2 Me), 3.36–3.31 (m, 4H, CH_2NCH_2), 3.81–3.76 (m, 4H, CH_2OCH_2), 4.62 (s, 1H, =CH); ^{13}C NMR: δ = 25.8, 48.0, 66.1, 82.0, 83.9, 172.3, 174.6; MS: *m/z* = 197 (92) [M^+], 182 (15), 126 (12), 124 (23), 112 (10), 111 (100), 82 (10), 81 (27), 53 (18). Anal. calcd. For $C_{10}H_{15}NO_3$ (197.23): C 60.90, H 7.67, N 7.10; found: C 61.03, H 7.65, N 7.11.

5-Ethyl-5-methyl-4-morpholin-4-yl-5*H*-furan-2-one (3ba): Yield: 1.38 g, starting from 824 mg of **1b** (78%, Table 2, entry 12). Colorless solid, mp 94–96 °C. IR (KBr): ν = 1714 (s), 1597 (s), 1319 (w), 1262 (w), 1228 (m), 1117 (m), 963 (m), 927 (m), 875 (m), 792 (m) cm^{-1}; ^1H NMR: δ = 0.90 (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 1.59 (s, 3H, $CH_3CCH_2CH_3$), 1.89–1.75 (m, 1H, $CHHCH_3$), 2.04–1.89 (m, 1H, $CHHCH_3$), 3.36–3.30 (m, 4H, CH_2NCH_2), 3.80–3.74 (m, 4H, CH_2OCH_2), 4.67 (s, 1H, =CH); ^{13}C NMR: δ = 7.8, 24.6, 31.2, 47.9, 66.2, 84.8, 85.3, 172.7, 172.8; MS: *m/z* = 211 (79) [M^+], 183 (100), 182 (84), 155 (19), 140 (27), 124 (37), 112 (28), 111 (89), 81 (15), 53 (23); anal. calcd. for $C_{11}H_{17}NO_3$ (211.26): C 62.54, H 8.11, N 6.63; found: C 62.67, H 8.09, N 6.62.

4-Morpholin-4-yl-1-oxaspiro[4.5]dec-3-en-2-one (3ca): Yield: 1.59 g, starting from 1.04 g of **1c** (80%, Table 2, entry 14). Colorless solid, mp 138–140 °C. IR (KBr): ν = 1723 (s), 1591 (s), 1319 (w), 1270 (w), 1242 (w), 1209 (m), 1120 (m), 975 (m), 951 (m), 881 (w), 781 (w) cm^{-1}; ^1H NMR: δ = 1.32–1.12 (m, 1H on cyclohexyl ring), 1.92–1.66 (m, 9H on cyclohexyl ring), 3.40–3.35 (m, 4H, CH_2NCH_2), 3.80–3.75 (m, 4H, CH_2OCH_2), 4.64 (s, 1H, =CH); ^{13}C NMR: δ = 22.0, 24.4, 33.8, 48.3, 66.2, 84.1, 84.6, 172.6, 174.5; MS: *m/z* = 237 (100) [M^+], 194 (26), 182 (9), 181 (46), 111 (77), 81 (11), 55 (12), 53 (14); anal. calcd. for $C_{13}H_{19}NO_3$ (237.29): C 65.80, H 8.07, N 5.90; found: C 65.69, H, 8.08, N, 5.88.

5-Ethyl-4-morpholin-4-yl-5*H*-furan-2-one (3da): Yield: 1.36 g, starting from 710 mg of **1d** (82%, Table 2, entry 16). Colorless solid, mp 125–126 °C. IR (KBr): ν = 1718 (s), 1609 (s), 1317 (w), 1273 (w), 1243 (m), 1167 (m), 1112 (m), 988 (m), 913 (w), 864 (m), 789 (m) cm^{-1}; ^1H NMR: δ = 1.01 (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 1.71–1.53 (m, 1H, $CHHCH_3$), 2.07–1.92 (m, 1H, $CHHCH_3$), 3.33–3.19 (m, 4H, CH_2NCH_2), 3.77 (t, *J* = 4.9 Hz, 4H, CH_2OCH_2), 4.71 (s, 1H, =CH), 4.91 (dd, *J* = 6.8, 3.0 Hz, 1H, OCH); ^{13}C NMR: δ = 8.5, 26.7, 47.9, 66.0, 78.4, 84.8, 171.1, 174.0; MS: *m/z* = 197 (58), [M^+], 169 (100), 168 (82), 141 (51), 140 (39), 111 (22), 110 (27), 82 (28), 68 (15), 55 (18), 53 (20); anal. calcd. for $C_{10}H_{15}NO_3$ (197.23): C 60.90, H 7.67, N 7.10; found: C 61.05, H 8.68, N 7.10.

4-Morpholin-4-yl-5-phenylethyl-5*H*-furan-2-one (3ea): Yield: 1.87 g, starting from 1.35 g of **1e** (81%, Table 2, entry 18). Colorless solid, mp 114–115 °C. IR (KBr): ν = 1716 (s), 1590 (s), 1351 (m), 1317 (w), 1247 (w), 1185 (m), 1115 (m), 1025 (m), 971 (w), 869 (w), 778 (m) cm^{-1}; ^1H NMR: δ = 1.97–1.82 (m, 1H, $CHHCH_2Ph$), 2.23–2.09 (m, 1H, $CHHCH_2Ph$), 2.92–2.71 (m, 2H, CH_2Ph), 3.17–3.03 (m, 4H, CH_2NCH_2), 3.68 (t, *J* = 4.9 Hz, 4H, CH_2OCH_2), 4.70 (s, 1H, =CH), 4.84 (dd, *J* = 8.3, 2.5 Hz, 1H, OCH), 7.24–7.17 (m, 3H on phenyl ring), 7.33–7.25 (m, 2H on phenyl ring); ^{13}C NMR: δ = 30.8, 35.9, 47.7, 65.9, 76.4, 84.7, 126.3, 128.6, 140.5, 171.4, 173.8; MS: *m/z* = 273 (1) [M^+], 170 (10), 169 (100), 141 (48), 140 (9), 112 (10), 111 (7), 91 (11); anal. calcd. for $C_{16}H_{19}NO_3$ (273.33): C 70.31, H 7.01, N 5.12; found: C 70.46, H 6.99, N 5.11.

5,5-Dimethyl-4-piperidin-1-yl-5*H*-furan-2-one (3ab): Yield: 1.32 g, starting from 708 mg of **1a** (80%, Table 2, entry 19). Pale yellow solid, mp 100–102 °C. IR (KBr): ν = 1719 (s), 1579 (s), 1256 (w), 1209 (m), 972 (m), 935 (w), 787 (m) cm^{-1}. ^1H NMR: δ = 1.61 (s, 6H, $OCMe_2$), 1.78–1.55 (m, 6H, $NCH_2CH_2CH_2CH_2$), 3.36–3.29 (m, 4H, CH_2NCH_2), 4.52 (s, 1H, =CH); ^{13}C NMR: δ = 23.8, 25.6, 25.7, 49.4, 81.7, 81.9, 172.9, 174.3; MS: *m/z* = 195 (55) [M^+], 194 (6), 180 (20), 124 (6), 110 (8), 109 (100), 108 (14), 68 (6), 55 (6), 53 (6); anal. calcd. for $C_{11}H_{17}NO_2$ (195.26): C 67.66, H 8.78, N 7.17; found: C 67.78, H 8.76, N 7.16.

5-Phenylethyl-4-piperidin-1-yl-5*H*-furan-2-one (3eb): Yield: 1.78 g, starting from 1.35 g of **1e** (78%, Table 2, entry 20). Pale yellow oil. IR (neat): ν = 2936 (m), 2856 (m), 1729 (s), 1603 (s), 1451 (m), 1247 (w), 1179 (m), 1042 (w), 1022 (w), 854 (w), 777 (m), 701 (m) cm^{-1}; ^1H NMR: δ = 1.73–1.48 (m, 6H, $NCH_2CH_2CH_2CH_2$), 1.97–1.80 (m, 1H, $CHHCH_2Ph$), 2.22–2.08 (m, 1H, $CHHCH_2Ph$), 2.90–2.71 (m, 2H, CH_2Ph), 3.15–3.03 (m, 4H, CH_2NCH_2), 4.62 (s, 1 H, =CH), 4.82 (dd, *J* = 8.3, 2.5 Hz, 1H, OCH), 7.24–7.16 (m, 3H on phenyl ring), 7.33–7.25 (m, 2H on phenyl ring); ^{13}C NMR: δ = 23.7, 25.3, 30.9, 35.9, 48.9, 76.5, 82.7, 126.2, 128.5, 140.7, 168.2, 171.3; MS: *m/z* = 271 (2) [M^+], 168 (10), 167 (100), 139 (60), 138 (22), 110 (12), 91 (10), 55 (6); anal. calcd. for $C_{17}H_{21}NO_2$ (271.35): C 75.25, H 7.80, N 5.16; found: C 75.18, H 7.78, N 5.17.

4-Diethylamino-5,5-dimethyl-5*H*-furan-2-one (3ac): Yield: 0.94 g, starting from 0.72 g of **1a** (60%, Table 2, entry 21). Pale yellow solid, mp 60–63 °C. IR (KBr): ν = 1706 (s), 1590 (s), 1284 (w), 1251 (m), 1200 (m), 986 (m), 937 (m), 792 (m) cm^{-1}; ^1H NMR: δ = 1.22 [t, *J* = 7.1 Hz, 6H, $N(CH_2CH_3)_2$], 1.61 (s, 6H, $OCMe_2$), 3.30 [q, *J* = 7.1 Hz, 4H, $N(CH_2CH_3)_2$], 4.46 (s, 1 H, =CH); ^{13}C NMR: δ = 12.9, 25.8, 44.8, 81.3, 81.8, 173.0, 173.7; MS: *m/z* = 183 (82) [M^+], 168 (100), 155 (11), 98 (12), 97 (97), 96 (23), 82 (80), 69 (75), 68 (56), 67 (12), 56 (14), 55 (12), 54 (13); anal. calcd. for $C_{10}H_{17}NO_2$ (183.25): C 65.54, H 9.35, N 7.64; found: C 65.43, H 9.33, N 7.66.

4-Diethylamino-5-ethyl-5-methyl-5*H*-furan-2-one (3bc): Yield: 0.98 g, starting from 0.84 g of **1b** (58%, Table 2, entry 22). Pale yellow solid, mp 62–65 °C. IR (KBr): ν = 2973 (m), 2935 (w), 1727 (s), 1591 (s), 1454 (m), 1281 (w), 1227 (m), 1196 (w), 962 (m), 778 (m) cm^{-1}; ^1H NMR: δ = 0.88 (t, *J* = 7.3 Hz, 3H, $OCCH_2CH_3$), 1.22 [t, *J* = 7.1 Hz, 6H, $N(CH_2CH_3)_2$], 1.60 (s, 3H, $OCCH_3$), 2.04–1.80 (m, 2H, $OCCH_2CH_3$), 3.33 [q, *J* = 7.1 Hz, 4H, $N(CH_2CH_3)_2$], 4.49 (s, 1H, =CH); ^{13}C NMR: δ = 7.7, 12.8 (br), 24.8, 31.0, 44.7, 82.5, 84.6, 171.7, 173.1; MS: *m/z* = 197 (66) [M^+], 182 (48), 169 (60), 168 (58), 150 (7), 141 (38), 140 (11), 138 (10), 126 (22), 124 (11), 113 (9), 110 (9), 98 (20), 97 (100), 96 (23), 82 (63), 69 (42), 68 (46), 56 (21); anal. calcd. for

$C_{11}H_{19}NO_2$ (197.27): C 66.97, H 9.71, N 7.10; found: C 67.12, H 9.70, N 7.08.

4-Diethylamino-1-oxaspiro[4.5]dec-3-en-2-one (3cc): Yield: 1.08 g, starting from 1.05 g of **1c** (57%, Table 2, entry 23). Colorless solid, mp 110–112 °C. IR (KBr): ν = 2971 (m), 2942 (m), 1719 (s), 1579 (s), 1344 (w), 1209 (m), 972 (m), 787 (m) cm^{-1}; ^1H NMR δ = 1.20 [t, *J* = 7.1 Hz, 6H, $N(CH_2CH_3)_2$], 1.34–1.14 (m, 1H on cyclohexyl ring), 1.94–1.63 (m, 9H on cyclohexyl ring), 3.32 [q, *J* = 7.1 Hz, 4H, $N(CH_2CH_3)_2$], 4.49 (s, 1 H, =CH); ^{13}C NMR: δ = 13.0, 22.2, 24.6, 33.9, 45.0, 82.5, 83.9, 173.3, 173.6; MS: *m/z* = 223 (93) [M^+], 208 (56), 180 (18), 167 (24), 152 (16), 139 (12), 124 (13), 97 (100), 96 (18), 85 (13), 82 (42), 69 (19), 68 (35); anal. calcd. for $C_{13}H_{21}NO_2$ (223.21): C 69.92, H 9.48, N 6.27; found: C 70.04, H 9.46, N 6.26.

4-Diethylamino-5-ethyl-5*H*-furan-2-one (3dc): Yield: 0.93 g, starting from 0.71 g of **1c** (60%, Table 2, entry 24). Colorless solid, mp 47–48 °C. IR (KBr): ν = 2973 (m), 2936 (m), 2877 (w), 1731 (s), 1601 (s), 1433 (m), 1329 (m), 1265 (w), 1169 (m), 985 (w), 907 (w), 774 (m) cm^{-1}; ^1H NMR: δ = 0.98 (t, *J* = 7.3 Hz, 3H, $OCHCH_2CH_3$), 1.21 (t, *J* = 7.1 Hz, 6H, $N(CH_2CH_3)_2$], 1.73–1.57 (m, 1H, $OCHCHHCH_3$), 2.08–1.94 (m, 1H, $OCHCHHCH_3$), 3.35–3.12 [m, 4H, $N(CH_2CH_3)_2$], 4.58 (s, 1H, =CH), 4.91 (dd, *J* = 6.4, 2.9 Hz, 1H, OCH); ^{13}C NMR: δ = 7.8, 12.4 (br), 26.1, 44.2, 78.0, 82.0, 169.6, 174.5; MS: *m/z* = 183 (95) [M^+], 168 (83), 155 (100), 154 (91), 127 (69), 126 (57), 112 (20), 98 (22), 97 (28), 82 (44), 70 (47), 69 (32), 68 (48), 56 (18); anal. calcd. for $C_{10}H_{17}NO_2$ (183.25): C 65.54, H 9.35, N 7.64; found: C 65.71, H 9.33, N 7.64.

4-Diethylamino-5-phenylethyl-5*H*-furan-2-one (3ec): Yield: 1.43 g, starting from 1.36 g of **1e** (65%, Table 2, entry 25). Pale yellow solid, mp 53–55 °C. IR (KBr): ν = 1715 (s), 1603 (s), 1342 (m), 1181 (m), 1081 (m), 1034 (m), 937 (w), 912 (w), 781 (m), 701 (m) cm^{-1}; ^1H NMR: δ = 1.15 [t, *J* = 7.3 Hz, 6H, $N(CH_2CH_3)_2$], 1.95–1.81 (m, 1H, $CHHCH_2Ph$), 2.23–2.10 (m, 1H, $CHHCH_2Ph$), 2.88–2.72 (m, 2H, CH_2Ph), 3.23–2.99 [m, 4H, $N(CH_2CH_3)_2$], 4.58 (s, 1H, =CH), 4.83 (dd, *J* = 7.9, 2.4 Hz, 1H, OCH), 7.33–7.16 (m, 5H, Ph); ^{13}C NMR: δ = 12.5 (br), 30.6, 35.7, 44.2, 76.3, 82.0, 126.0, 128.27, 128.34, 140.4, 170.2, 174.3; MS: *m/z* = 259 (1) [M^+], 156 (10), 155 (100), 127 (50), 112 (24), 98 (10), 91 (15), 70 (15), 68 (12); anal. calcd. for $C_{16}H_{21}NO_2$ (259.34): C 74.10, H 8.16, N 5.40; found: C 74.21, H 8.17, N 5.39.

4-Morpholin-4-yl-5-(2,4,6-trimethylphenyl)-5*H*-furan-2-one (3fa): Yield: 1.48 g, starting from 1.46 g of **1f** (61%, Table 2, entry 26). Pale yellow solid, mp 178–180 °C. IR (KBr): ν = 1733 (s), 1616 (s), 1433 (m), 1301 (w), 1157 (m), 1112 (w), 1005 (w), 765 (m), 707 (w) cm^{-1}; ^1H NMR: δ = 2.22 (s, 3H, Me), 2.25 (s, 3H, Me), 2.43 (s, 3H, Me), 2.97–3.22 (m, 4H, CH_2NCH_2), 3.41–3.66 (m, 4H, CH_2OCH_2), 4.86 (s, 1H, =CH), 6.12 (s, 1H, OCH), 6.81 (s, 1H aromatic), 6.87 (s, 1H aromatic); ^{13}C NMR: δ = 19.4, 20.6, 20.9, 47.3, 65.9, 76.5, 84.9, 127.3, 129.9, 131.4, 137.4, 138.5, 139.3, 171.3, 173.9; MS: *m/z* = 287 (53) [M^+], 258 (10), 245 (23), 244 (67), 229 (87), 228 (100), 207 (11), 174 (23), 158 (17), 141 (15), 128 (15), 119 (18), 115 (25), 112 (45), 111 (99), 91 (28), 86 (28), 81 (27), 77 (16), 68 (13), 57 (16), 55 (22), 53 (48); anal. calcd. for $C_{17}H_{21}NO_3$ (287.35): C 71.06, H 7.37, N 4.87; found: C 71.28, H 7.36, N 4.88.

4-Hydroxy-4-methyl-1-morpholin-4-ylpent-2-ynone (4aa): Yield: 299 mg starting from 351 mg of **1a** (36%, Table 1, entry 1). Pale yellow solid, mp 75–77 °C. IR (KBr): ν = 3410 (m, br), 2221 (m), 1609 (s), 1439 (m), 1275 (m), 1253 (m), 1171 (m), 1112 (m), 955 (m), 845 (w), 732 (w) cm^{-1}; ^1H NMR: δ = 1.56 (s, 6H, 2 Me), 3.77–3.60 (m, 8H, 2 OCH_2CH_2N); ^{13}C NMR: δ = 30.7, 41.9, 47.3, 64.7, 66.4, 66.8, 73.7, 97.4, 153.1; MS: *m/z* = 197 (33) [M^+], 182 (42), 164 (18), 150 (20), 140 (19), 110 (11), 109 (12), 94 (15), 86 (100), 80 (29), 59 (25), 56 (73), 53 (86); anal. calcd. for $C_{10}H_{15}NO_3$ (197.23): C 60.90, H 7.67, N 7.10; found: C 60.79, H 7.69, N 7.11.

(*Z*)-2-(1-Hydroxy-1-methylethyl)-1,4-dimorpholin-4-ylbut-2-ene-1,4-dione 5aa: Yield: 207 mg , starting from 351 mg of **1a** (16%, Table 1, entry 1). Pale yellow solid, mp 120–122 °C. IR (KBr): ν = 3429 (m, br), 1632 (s), 1608 (s), 1433 (s), 1271 (m), 1247 (m), 1112 (s), 583 (m), 560 (m) cm^{-1}; ^1H NMR: δ = 1.44 (s, 3H, Me), 1.46 (s, 3H, Me), 3.82–3.29 (m, 16H, 4 NCH_2CH_2O), 6.30 (s, 1H, =CH); ^{13}C NMR: δ = 29.1, 30.1, 41.6, 41.9, 46.8, 47.3, 66.5, 66.7, 66.8, 71.9, 117.1, 151.1, 165.2, 168.2 ppm. MS: *m/z* = 312 (< 0.5) [M^+], 253 (4), 227 (13), 226 (76), 210 (22), 209 (100), 114 (15), 96 (10), 86 (28), 70 (14), 59 (9), 56 (7); anal. calcd. for $C_{15}H_{24}N_2O_5$ (312.36): C 57.68, H 7.74, N 8.97; found: C 57.81, H 7.73, N 8.98.

X-Ray Crystallographic Study

Crystal data for **3aa**: $C_{10}H_{15}NO_3$, M_r = 197.2, monoclinic, *Pn*, *a* = 6.320(2), *b*=9.961(4), *c* = 8.338(2) Å, β = 104.91(2)°, *V* = 507.3(3) $Å^3$, *Z* = 2, ρ_{calc} = 1.291 gcm^{-3}, μ(Mo Kα) = 0.095 cm^{-1}, *F*(000) = 212, crystal size = 0.34 × 0.28 × 0.22 mm, *T* = 298 K, $2\theta_{max}$ = 50.1°, 987 independent reflections , 128 variable parameters, R_1 = 0.0385 ($I > 2\sigma(I)$), wR_2 = 0.1010, GOF(F^2) = 0.945, max/min residual electron density 0.138/ −0.118 e $Å^{-3}$.

White crystals of **3aa** were crystallized at room temperature from a chloroform solution. Data collection was carried out at room temperature on a Siemens *R3 m/v* diffractometer using graphite-monochromated MoKα (λ = 0.71073 Å) radiation. The data were corrected for Lorentz and polarization effects. Absorption correction was applied (XABS2).[15] Since it was not possible to distinguish between the *Pn* and *P*2/*n* space groups from the analysis of the systematic absences, attempts to solve the structure in both acentric and centric systems were made. The best solution was found in the *Pn* space group. The structure solution and full-matrix least-squares refinements based on F^2 were performed with XS and XL routines in the SHELXTL-NT program package. All non-hydrogen atoms were refined anisotropically and Hydrogen atoms were included as idealized atoms riding on the respective carbon atoms, with C–H bond lengths appropriate to the atom hybridization.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-220001. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

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