##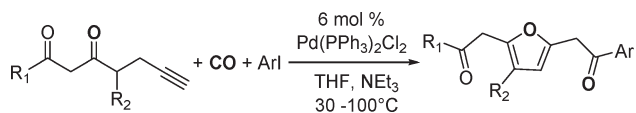 Palladium-Catalyzed Carbonylative Cycloisomerization of γ-Propynyl-1,3-diketones: A Concise Route to Polysubstituted Furans

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Di- and trisubstituted furan derivatives have been efficiently synthesized via palladium(II)-catalyzed intramolecular carbonylative cycloisomerization of γ-propynyl-1,3-diketones with aryl iodides and carbon monoxide. The mechanism suggests that *in situ* generated acylpalladium species from the carbonylation of aryl iodide initiates the reaction followed by cyclization of the enolized isomer of a 1,3-diketone substrate via carbon–carbon triple bond activation.

Highly substituted furans have been found as key structural units in many biologically important natural products and pharmaceuticals.[1] Substituted furans are usually synthesized by functionalization of an existing furan ring,[2] through cycloisomerization of alkynyl- and allenyl-functionalized compounds,[3] or by means of alkyne- and allene-involved reactions.[4] 1,3-Dicarbonyl compounds have also been used in the synthesis of furans,[5] but only a few examples involving α-propargyl β-ketoesters have been known for construction of polysubstituted furans.[6] Although these methods have been successfully applied in the synthesis of furan derivatives, they are usually used with limitation such as the difficulty accessing polyfunctionalized furans. Thus, synthesis of polysubstituted furans remains a challenge in organic synthesis. As a continuation of our interest in the carbonylative coupling of alkynes and 1,3-dicarbonyl compounds,[7] we investigated the carbonylation of γ-propynyl-1,3-dicarbonyl compounds with carbon monoxide in the presence of an organic halide. Herein, we report synthesis of di- and trisubstituted furans through concise carbonylative cycloisomerization of γ-propynyl-1,3-diketones.

In our initial study, carbonylation of 1,3-diketone **1a** in the presence of iodobenzene **2a** was tried in THF with 3 mol % Pd(PPh$_3$)$_2$Cl$_2$ as the precatalyst (Table 1, entries 1−4), affording the desired product **3a** in up to 73% yield, while the possible product of type **3a′** was not detected.[6a] With 6 mol % catalyst, **3a** was obtained in 77% yield (entry 5). Decreasing the base amount from 5 to 1 equiv led to **3a** in a lower yield (72%, entries 5−7). A CO pressure of 200 psi seems to be suitable for the reaction, and the expected reaction worked less efficiently with atmospheric CO (entry 11). Unexpectedly, the reaction proceeded more efficiently at a relatively low temperature such as 30 °C (entry 13). Under the same conditions, PdCl$_2$, PdCl$_2$/PPh$_3$, and Pd(OAc)$_2$ exhibited no catalytic activity (entries 14−16). The first and the last precatalysts failed presumably as a result of the absence of ligand, and the middle case may have resulted from the incorrect stoichiometry of ligand and/or inadequate time for an active catalytic species to form before addition of the substrates. Pd(0) precatalysts Pd(dba)$_2$ and Pd(PPh$_3$)$_4$ showed no or very poor activity for the desired reaction. In the presence of dppb ligand, Pd(OAc)$_2$ exhibited a low activity in water (entry 19), and in ionic liquid [bmin]PF$_6$, Pd(PPh$_3$)$_2$Cl$_2$ could only demonstrate a poor catalytic activity (entry 20). It is worth noting that the reaction of **1a** and **2a** to form **3a** should be carried out under CO atmosphere, and a catalyst and base such as Et$_3$N are essential for the reaction.

To define the protocol scope, different types of γ-propynyl-1,3-diketones were applied as the substrates. γ-Functionalization[8] was employed to modify the skeleton of a 1,3-diketone. Thus, treatment of a 1,3-diketone with 2 equiv of LDA followed by reaction with an electrophile, e.g., propargyl bromide, may produce two new isomeric γ-functionalized 1,3-diketones via the *in situ* generated doubly enolized dianions (see Experimental Section). Starting from symmetrical 1,3-dialkyl-1,3-diones and unsymmetrical 1-aryl-3-alkyl-1,3-diones, only one type of γ-functionalization products such as **1a**, **1m**, and **1n** were obtained (Table 2).[9]

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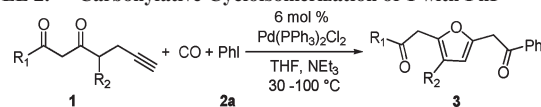(9) Kel'in, A. V.; Maioli, A. *Curr. Org. Chem.* **2003**, *7*, 1855.

TABLE 1. Screening of Reaction Conditions[a]
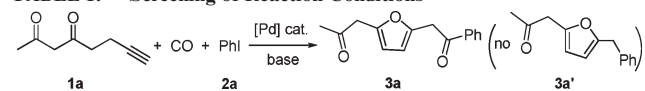
entry	catalyst/mol %	solvent (5 mL)	NEt₃ (equiv)	P(CO) (psi)	temp (°C)	yield[b] (%)
1	Pd(PPh₃)₂Cl₂/3	CH₃CN	5	200	100	36
2	Pd(PPh₃)₂Cl₂/3	DME	5	200	100	55
3	Pd(PPh₃)₂Cl₂/3	NEt₃	36	200	100	66
4	Pd(PPh₃)₂Cl₂/3	THF	5	200	100	73
5	Pd(PPh₃)₂Cl₂/6	THF	5	200	100	77
6	Pd(PPh₃)₂Cl₂/6	THF	2	200	100	76
7	Pd(PPh₃)₂Cl₂/6	THF	1	200	100	72
8	Pd(PPh₃)₂Cl₂/6	THF	2	400	100	75
9	Pd(PPh₃)₂Cl₂/6	THF	2	100	100	73
10	Pd(PPh₃)₂Cl₂/6	THF	2	50	100	69
11	Pd(PPh₃)₂Cl₂/6	THF	2	14.7	60	62
12	Pd(PPh₃)₂Cl₂/6	THF	2	200	60	78
13	**Pd(PPh₃)₂Cl₂/6**	**THF**	**2**	**200**	**30**	**79**
14	PdCl₂/6	THF	2	200	30	0
15	PdCl₂/6; PPh₃/12	THF	2	200	30	< 1
16	Pd(OAc)₂/6	THF	2	200	30	0
17	Pd(dba)₂/6	THF	2	200	30	0
18	Pd(PPh₃)₄/6	THF	2	200	30	< 10
19	Pd(OAc)₂/6; dppb/6	H₂O	2	200	100	40
20	Pd(PPh₃)₂Cl₂/6	[bmin]PF₆	5	200	100	31

[a]Conditions: **1a**, 1.0 mmol; **2a**, 1.0 mmol; 4 h. [b]Isolated yields of **3a**. dppb = 1,4-bis(diphenylphosphino)butane.

Using unsymmetical 1,3-dialkyl-1,3-diones, which can be deprotonated at two different γ-positions, their γ-functionalization usually afforded a mixture of two inseparable isomers such as **1d**/**1d′**, **1e**/**1e′**, and **1f**/**1f′** (substrates for entries 4−6, Table 2). A bulky substituent such as isopropyl and cyclopentyl at the γ-position excluded double γ-functionalization, exclusively leading to a mono-γ-functionalization product, e.g., **1b** and **1c** (substrates for entries 2 and 3, Table 2).[10] Only in one case, isomeric **1g** and **1h** were successfully separated by flash silica gel column chromatography (substrates for entries 7 and 8, Table 2).

Under the optimized conditions for carbonylative cycloisomerization, the reactions of **1b** and **1c** afforded the desired products **3b** and **3c** in 43−57% yields (Table 2, entries 2 and 3). Although a mixture of two inseparable γ-stereoisomers was used as the substrate, both of the isomers were reactive to undergo the expected reactions, forming two separable products in moderate to good yields (entries 4−6). The reactions of isomeric **1g** and **1h** gave the desired products **3g** and **3h** in 56−67% yields (entries 7 and 8), respectively. Fused furan **3i** was obtained from the reaction of cyclic substrate **1i**[11] (entry 9). The enamine of **1a**, i.e., **1j**, also underwent the reaction to form **3a** as the product (entry 10). No reaction was observed for internal alkyne **1k** and β-ketoester **1l** (entries 11 and 12), presumably due to the steric hindrance of the terminal alkyl of **1k** and change of the enolization of **1l** by replacing acetyl with an ester moiety. Carbonylation products **3m** and **3n** instead of the desired products were obtained in 36% and 38% yields from the reactions of **1m** and **1n** with CO and PhI, respectively (eq 1), suggesting that the linker between a carbonyl and its adjacent

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TABLE 2. Carbonylative Cycloisomerization of 1 with PhI[a]

entry	alkyne	product	yield[b] (%)
1	**1a**	**3a**	79[c]
2	**1b**	**3b**	43[c,d]
3	**1c**	**3c**	57[c,d]
4	**1d + 1d′** (2.5:1)	**3d**	54
		3d′	18
5	**1e + 1e′** (2.8:1)	**3e**	53
		3e′	16
6	**1f + 1f′** (3.4:1)	**3f**	71
		3f′	7
7	**1g**	**3g**	67
8	**1h**	**3h**	56
9	**1i**	**3i**	44[c]
10	**1j**	**3a**	44
11	**1k**	**3k**	0
12	**1l**	**3l**	0

[a]Conditions: **1**, 1.0 mmol; PhI, 1.0 mmol; Pd(PPh₃)₂Cl₂, 6 mol %; NEt₃, 2.0 mmol; THF, 5.0 mL; P(CO), 200 psi; 30 °C; 8 h. [b]Isolated yields. [c]4 h. [d]100 °C.

alkynyl plays a key role in directing formation of the target products, and the linker length should be two CH₂ groups. Substrate **1o** was decomposed to the cyclization product **3o** (eq 2), revealing that replacement of 1-alkyl with an aryl changes the enolization mode of a 1,3-diketone moiety in the substrate and thus alters the reaction pathway.

$$\textbf{1m} (n = 3) \quad \textbf{1n} (n = 4) + CO + PhI \xrightarrow[\substack{THF, NEt_3 \\ 30\ ^\circ C,\ 4\ h}]{\substack{6\ mol\ \% \\ Pd(PPh_3)_2Cl_2}} \textbf{3m} (n = 3),\ 36\% \quad \textbf{3n} (n = 4),\ 38\% \quad (1)$$

$$\textbf{1o} + CO + PhI \xrightarrow[\substack{THF, NEt_3 \\ 30\ ^\circ C,\ 4\ h}]{\substack{6\ mol\ \% \\ Pd(PPh_3)_2Cl_2}} \textbf{3o},\ 20\% \quad (2)$$
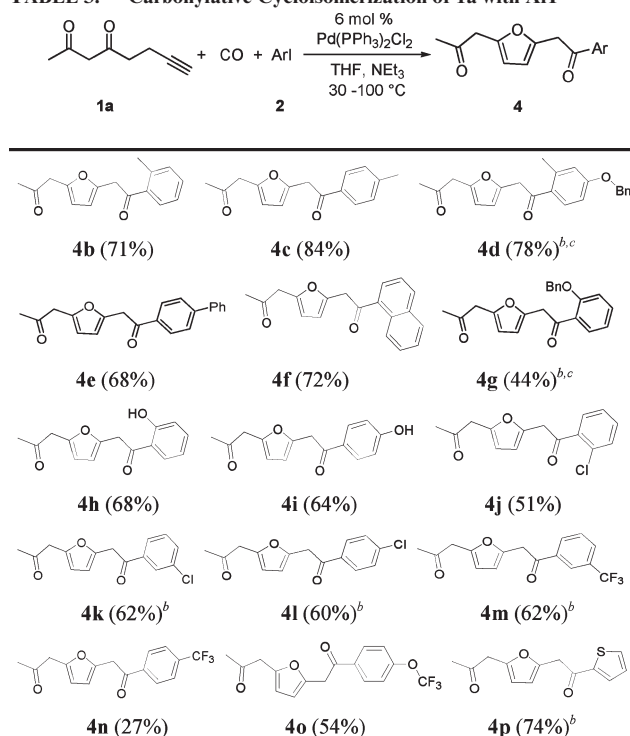
Next, the synthetic procedure was extended to the reactions of **1a** with a variety of aryl iodides, producing 2,5-disubstituted furans **4b–p** in good to excellent yields (Table 3). An electron-donating substituent such as a methyl in ArI facilitates formation of the desired products **4b–d** (71–84%), whereas electron-withdrawing substituents decreased the reaction efficiency, leading to **4j–o** in lower yields (27–62%). The steric hindrance from a 2-substituent in ArI retarded the reactions. The reaction of 2-iodothiophene gave the target product **4p** in 74% yield.

SCHEME 1. Proposed Mechanism
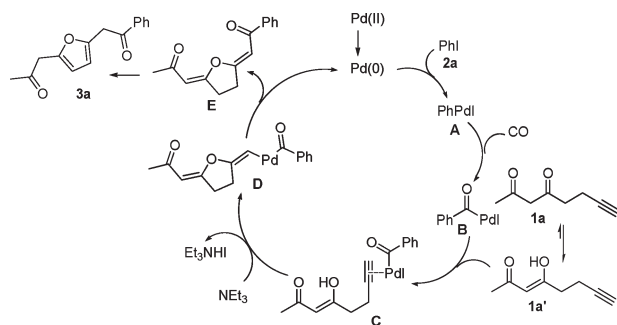
A plausible mechanism is demonstrated by the reaction of **1a**, **2a**, PhI, and CO in Scheme 1.[5a,6a] The reaction is presumably initiated by reduction of Pd(PPh$_3$)$_2$Cl$_2$ to the Pd(0) species,[12] followed by oxidative addition of aryl iodide **2a** to form intermediate **A**, which undergoes CO insertion to generate acylpalladium complex **B**. Enolized **1a**, i.e., **1a′**, is then activated through coordination to the metal by its C≡C bond to form species **C**. Intramolecular nucleophilic attack of the enolic oxygen across the activated C≡C bond gives Pd(II) species **D**. Subsequent reductive elimination affords dialkylidene intermediate **E** and regenerates the Pd(0) species.[13] Spontaneous isomerization of **E**[5a,6a] forms the carbonylative cycloisomerization product, i.e., 2,5-disubstituted furan **3a**. The carbonylative cycloisomerization of **1** in the presence of **2** may also proceed through other mechanisms. Carbonylative Sonogashira reactions of aryl iodides and terminal alkynes have been known to form alkynyl aryl ketones,[14] and ynones can be transformed to furans under gold[15] or acid[16] catalysis. In our case, the target products could be produced from the cyclization of the presumably generated ynone species similar to **3m** or **3n** with a (CH$_2$)$_2$ linker.

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TABLE 3. Carbonylative Cycloisomerization of 1a with ArI[a]

4b (71%)   **4c** (84%)   **4d** (78%)[b,c]

4e (68%)   **4f** (72%)   **4g** (44%)[b,c]

4h (68%)   **4i** (64%)   **4j** (51%)

4k (62%)[b]   **4l** (60%)[b]   **4m** (62%)[b]

**4n** (27%)   **4o** (54%)   **4p** (74%)[b]

[a]Conditions: **1a**, 1.0 mmol; ArI, 1.0 mmol; Pd(PPh$_3$)$_2$Cl$_2$, 6 mol %; NEt$_3$, 2.0 mmol; THF, 5.0 mL; P(CO), 200 psi; 100 °C, 8 h. Isolated yields in parentheses. [b]4 h. [c]30 °C.

In conclusion, a concise protocol has been developed to synthesize di- and trisubstituted furans. The proposed mechanism suggests that the reaction proceeds through Pd-catalyzed carbonylation of an aryl iodide followed by cyclization of the enolized isomer of γ-propynyl-1,3-diketone *via* carbon–carbon triple bond activation.

Experimental Section

γ-Functionalization of 1,3-Diketones. γ-Propynyl-1,3-diketones were synthesized using the reported procedures as shown in Scheme 2.[8] Treatment of 1,3-diketone **I** with 2 equiv of LDA at low temperature produces double enolization dianions **II/II′**, which can be further reacted with an electrophile such as propargyl bromide (**III**) to form two isomeric γ-functionalized 1,3-diketone products **IV** and **IV′**.

SCHEME 2. γ-Functionalization of 1,3-Diketones
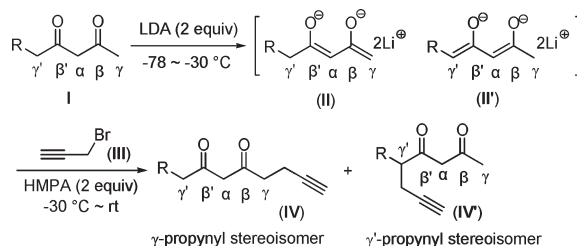
Typical Procedure for the Palladium-Catalyzed Carbonylative Cycloisomerization Reactions. Synthesis of 3a. Pd(PPh$_3$)$_2$Cl$_2$ (42 mg, 0.06 mmol), THF (5.0 mL), diketone **1a** (138 mg, 1.0 mmol),

iodobenzene **2a** (204 mg, 1.0 mmol), and triethylamine (202 mg, 2.0 mmol) were successively added to a 45 mL autoclave. The reactor was closed, purged three times with carbon monoxide, pressurized with 200 psi CO, and then heated at 30 °C for 4 h. The CO pressure was discharged at room temperature. All volatiles were removed under reduced pressure, and the resultant residue was purified by flash silica gel column chromatography (eluent, petroleum ether (60−90 °C)/EtOAc = 10:1 v/v) to afford 2,5-disubstituted furan **3a** as a pale yellow oil (190 mg, 79%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.97 (d), 7.54 (t), and

7.43 (t) (2:1:2 H, Ph), 6.18 (dd, J = 2.8 Hz, 1H, furyl CH), 6.14 (dd, J = 19.4 Hz, 1 H, furyl CH), 4.26 and 3.63 (s each, 2:2 H, $2 \times$ CH$_2$), 2.09 (s, 3 H, CH$_3$). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 204.2 and 194.8 (Cq each, C=O), 147.8 and 147.7 (Cq each, furyl C−O), 135.9 (Cq, *i*-C, Ph), 133.2, 128.5, and 128.3 (1:2:2 CH), 109.3 and 109.2 (1:1 CH, furyl), 43.0 and 38.2 ($2 \times$ CH$_2$), 28.8 (CH$_3$). HRMS (EI) calcd for C$_{15}$H$_{14}$O$_3$ [M$^+$] 242.0943, found 242.0949.

Supporting Information Available: Spectroscopic data and copies of ^{1}H, ^{13}C{^{1}H} and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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