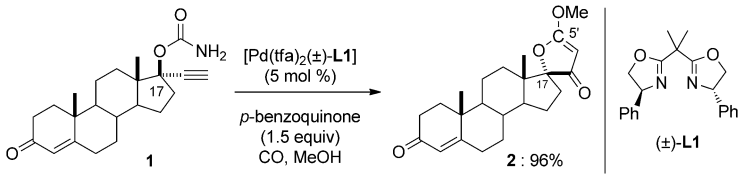
Communications

Synthetic Methods

T. Kusakabe, T. Takahashi, R. Shen, A. Ikeda, Y. D. Dhage, Y. Kanno, Y. Inouye, H. Sasai, T. Mochida, K. Kato* ——— ■■■■–■■■■



Carbonylation of Propargyl Carbamates with Palladium(II) Bisoxazoline Catalysts: Efficient Synthesis of 5-Methoxy-3(2*H*)-furanones

Palladium and CO: Carbonylation of **1** with [Pd(tfa)$_2$(±)-**L1**] (tfa = trifluoroacetate) affords the spirofuranone **2** with inversion of the stereochemistry at C17 in 96% yield. C17-*epi*-**1** also gave the same product **2** with retention of the stereochemistry at C17. Labelling studies show that ^{13}CO was incorporated into the C5′ position of the furanone ring. The first asymmetric version of this new reaction was achieved.

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Carbonylation of Propargyl Carbamates with Palladium(II) Bisoxazoline Catalysts: Efficient Synthesis of 5-Methoxy-3(2*H*)-furanones**

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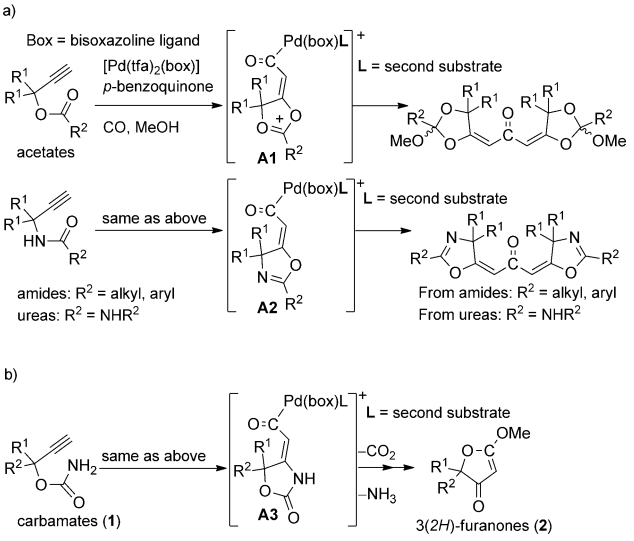
3(*2H*)-Furanones are well known as basic components of natural products which display a wide range of characteristic physiological properties.[1] A number of synthetic strategies[2] and pharmaceutically active substances[3] have been reported. The transition metal catalyzed reaction of unsaturated systems has recently proven to be a powerful method for the construction of a variety of carbo- and heterocycles.[4] Recently, we reported the cyclization/carbonylation/cyclization-coupling reaction (CCC-coupling reaction) of propargyl acetates, amides, ureas,[5a,b] γ-propynyl-1,3-diketones,[5c] N-propargylanilines, and *o*-alkynylphenols[5d] catalyzed by palladium(II) bisoxazoline (box) complexes (Scheme 1 a).

Symmetrical ketones bearing two oxazoles, cyclic orthoesters, oxabicyclic groups, quinolones, and benzofurans were obtained in a one-step procedure. The triple bond of the substrate coordinates to palladium(II) and undergoes nucleophilic attack by the intramolecular nucleophilic oxygen atom with subsequent CO insertion to produce either the acyl palladium intermediate **A1** or **A2**. Coordination of the triple bond of the second molecule induces the second cyclization. Reductive elimination then leads to formation of a ketone with two heterocyclic groups. In the absence of the box ligand, methanolysis of the acyl palladium intermediate ($L = MeO^-$, neutral complex) occurs predominantly. We believe that the box ligand enhances the π-electrophilicity of palladium(II),[5,6] and thus promotes coordination of the second triple bond to the acyl palladium intermediate **A1** or **A2**, thus leading to the dimerization reaction. At the same time, methanolysis of the acyl palladium intermediate **A1** or **A2** is suppressed by coordination of the second triple bond. To extend the concept of this tandem reaction, we planned to investigate the [(box)Pd^{II}]-catalyzed carbonylation reaction



Scheme 1. a) Previous work on CCC-coupling reaction. b) This work.

of analogous substrates, that is, carbamates **1** (Scheme 1 b). Based on our earlier results, the acyl palladium intermediate **A3** should be produced by a similar reaction of the carbamates **1**, and methanolysis of **A3** should be suppressed by coordination of the triple bond of a second molecule. If the rate of decarboxylation of **A3** is fast compared to that of the CCC-coupling reaction, a new type of cascade reaction is expected. Consequently, we report herein a new preparation of the 5-methoxy-3(2*H*)-furanones **2** by the cyclization/carbonylation/decarboxylation/cyclization sequence of the propargyl carbamates **1** catalyzed by [(box)Pd^{II}] complexes.

Initially, we selected **1a** as a standard substrate to search for potential catalysts (Table 1). The reaction of **1a** with $[(CH_3CN)_2PdCl_2]$ (5 mol%) in the presence of *p*-benzoquinone (1.5 equiv) in methanol under a carbon monoxide atmosphere (balloon) generated the acrylate **3a** in 40% yield along with a mixture of unidentified compounds (Table 1, entry 1). The structure of **3a** was determined by X-ray crystallographic analysis.[7,8] The use of $[(Ph_3P)_2PdCl_2]$ and $Pd(tfa)_2$ afforded **3a** in poor yields (entries 2 and 3). In addition, [{(−)-sparteine}Pd(tfa)$_2$] and [(2,2′-bipyridine)$PdCl_2$] did not show catalytic activity. An attempt was then made to use the box ligand according to our hypothesis, and thus resulted in a new reaction pathway to afford the 5-methoxy-3(2*H*)-furanones **2**. Although the use of the box ligands **L2** and **L3** (Figure 1) resulted in the formation of **2a** in

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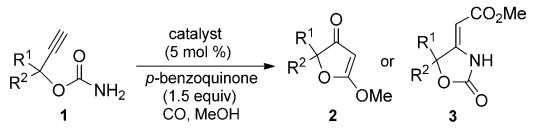
Table 1: Carbonylation of the carbamates **1**.



1 **2** **3**

Entry	R^1	R^2	t [h]	**2** Yield [%][a]	**3** Yield [%][a]
1[b,f]	**1a**: -$(CH_2)_5$-		18	**2a**: –	**3a**: 40
2[c,f]	**1a**: -$(CH_2)_5$-		24	**2a**: –	**3a**: 30
3[d,f]	**1a**: -$(CH_2)_5$-		23	**2a**: –	**3a**: 23
4[e,f]	**1a**: -$(CH_2)_5$-		22	**2a**: 60	**3a**: –
5[e,f]	**1b**: -$(CH_2)_6$-		17	**2b**: 68	**3b**: –
6[e,f]	**1c**: Me	$Ph(CH_2)_2$	22	**2c**: 72	**3c**: –
7[e,f]	**1d**: Me	$CH_3(CH_2)_4$	16	**2d**: 63	**3d**: –
8[e,g]	**1e**: Et	$CH_3(CH_2)_8$	3	**2e**: 60	**3e**: –
9[e,g]	**1f**: Me	*i*Bu	20	**2f**: 60	**3f**: –
10[e,g]	**1g**: Et	Et	4	**2g**: 60	**3g**: –
11[e,g]	**1h**: $CH_3(CH_2)_{10}$	$CH_3(CH_2)_{10}$	3	**2h**: 73	**3h**: –
12[e,g]	**1i**: $CH_3(CH_2)_{12}$	$CH_3(CH_2)_{12}$	3	**2i**: 73	**3i**: –
13[e,g]	**1j**: Me	Ph	21	**2j**: 58	**3j**: –

[a] Yield is that of isolated product. [b] $[(CH_3CN)_2PdCl_2]$ (5 mol%) was employed. [c] $Pd(tfa)_2$ (5 mol%) was employed. [d] $[(Ph_3P)_2PdCl_2]$ (5 mol%) was employed. [e] $[Pd(tfa)_2(\pm)$-**L1**$]$ (5 mol%) was employed. [f] 45 °C. [g] RT.

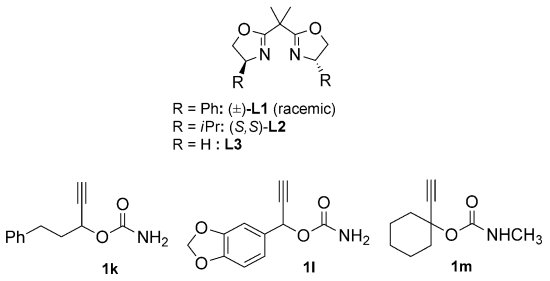
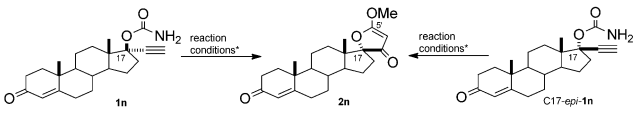


Figure 1. Ligands and additional substrates for Table 1.

lower yield (2–11%), $[Pd(tfa)_2($**L1**$)]$[5d] accelerated the reaction, and the yield improved to 60% (Table 1, entry 4).[9] The reaction of the seven-membered ring substrate **1b** and acyclic substrates **1c–i** containing two alkyl groups at the propargylic position occurred smoothly in the presence of the $[Pd(tfa)_2($**L1**$)]$, thus affording the 5-methoxy-3(2*H*)-furanones **2a–i** in 60–73% yields (Table 1, entries 5–12). The substrate **1j**, which possesses a phenyl group at the propargylic position, was also converted into **2j** in 58% yield (Table 1, entry 13). The *gem*-dialkyl effect[10] plays a fundamental role in the success of the reaction. Without it, the reactions of **1k** and **1l** did not proceed, and the N-methyl derivative **1m** gave the product **2a** in lower yield (27%; Figure 1). To investigate the reaction mechanism, preliminary control reactions were performed. In the absence of *p*-benzoquinone, the reaction gave **2a** in 3% yield along with recovery of **1a** (77%). In the absence of carbon monoxide, a complex mixture was obtained. These results suggested that the Pd^{II} species acted as the catalyst and carbon monoxide was incorporated in the product. In addition, the reaction of **3** under the same reaction conditions (Table 1, enties 4–7) did not proceed (recovery 99%), thus indicating that **3** is not an intermediate for producing **2**.

To elucidate the reaction mechanism, including the stereochemical course of the furanone ring formation, we investigated the reaction of the steroidal compound **1n** as a chiral substrate (Table 2). The reaction of **1n** proceeded

Table 2: Control reactions of steroid **1n**.[a]



Entry	Ligand (mol%)	$Pd(tfa)_2$ (mol%)	t [h]	**2n** Yield [%]
1	(*R*,*R*)-**L1** (7.5)	5	1	87
2	(*R*,*R*)-**L1** (15)	12	1	97
3[b]	(*R*,*R*)-**L1** (7.5)	5	1	92
4[c]	(*R*,*R*)-**L1** (7.5)	5	1	72
5	(*S*,*S*)-**L1** (15)	12	4	10
6[d]	$[Pd(tfa)_2(\pm)$-**L1**$]$	5	1.5	96

[a] Reaction conditions: Ligand, $Pd(tfa)_2$, *p*-benzoquinone (1.5 equiv), CO, MeOH, 45 °C. Yield is that of isolated product. [b] C17-epi-**1n** was used as substrate. [c] ^{13}CO was employed and it was incorporated into C5′ position of **2n**. [d] RT.

smoothly in the presence of $Pd(tfa)_2$/(*R*,*R*)-**L1**, thus affording the spirofuranone **2n** in good to excellent yield with inversion of the stereochemistry at C17 (Table 2, entries 1 and 2). The structure of **2n** was determined by X-ray crystallographic analysis.[7] Interestingly, the reaction of C17-*epi*-**1n**[11] using the same catalyst, $Pd(tfa)_2$/(*R*,*R*)-**L1**, afforded the same product **2n** in 92% yield with retention of the stereochemistry at C17 (Table 2, entry 3). Once the propargylic C–O bond is cleaved, an S_N1-type cyclization may occur from the less hindered α face to form the furanone ring. From the preliminary control reaction, carbon monoxide is indispensable to promote the reaction. We confirmed this result through ^{13}C-isotope labeling which showed that ^{13}CO was clearly incorporated into the C5′ position of the furanone ring (Table 2, entry 4). The reaction of **1n** in the presence of $Pd(tfa)_2$/(*S*,*S*)-**L1** scarcely proceeded, thus giving **2n** in 10% yield (Table 2, entry 5). These results (Table 2, entries 1 and 5) imply that the ligand control may strongly affect the stereochemical course of the cyclization. Fortunately, although half the amount of catalyst was ineffective, 5 mol% of the racemic complex $[Pd(tfa)_2(\pm)$-**L1**$]$ worked well (Table 2, entry 6).

Recently, steroidal compounds containing spiro-heterocycles have attracted much attention because of their characteristic physiological activities [e.g., saridegib[12a] (IPI-926, antineoplastic activity), hedgehog signaling inhibitors,[12b–e] mifepristone (RU 486, progesterone antagonist),[12f] selective estrogen receptor ligand,[12g] and selective androgen receptor modulator (SARM)[12h]]. Thus, we investigated the reaction of the steroidal carbamates **1o–t** in the presence of the racemic complex $[Pd(tfa)_2(\pm)$-**L1**$]$ (Figure 2). In all cases, the reaction proceeded well, and the spirofuranones **2o–t** were obtained in excellent yields.

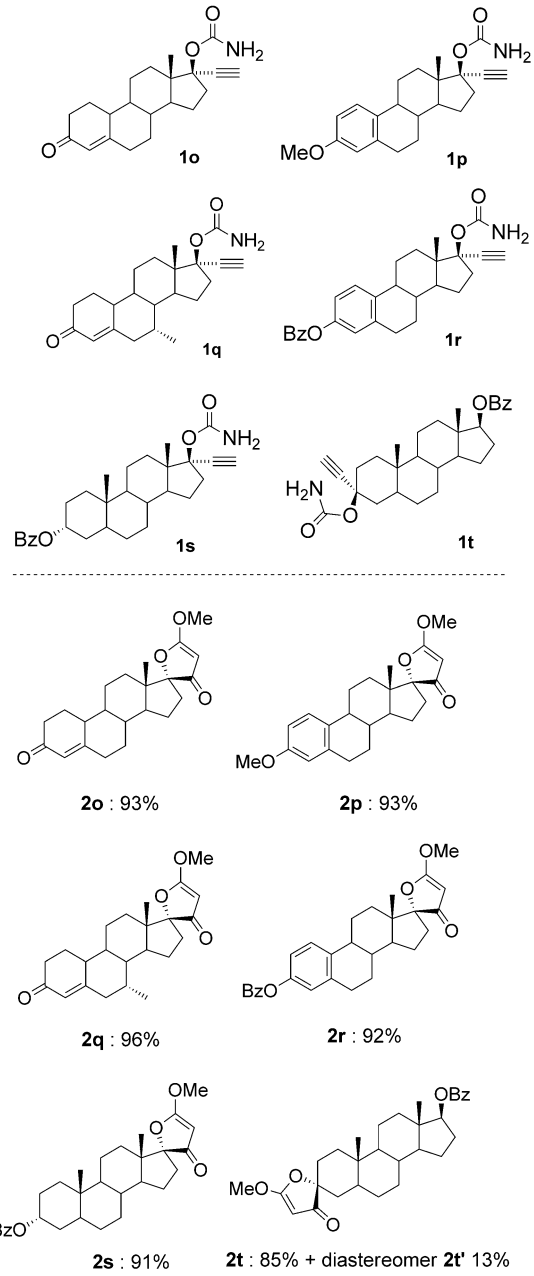
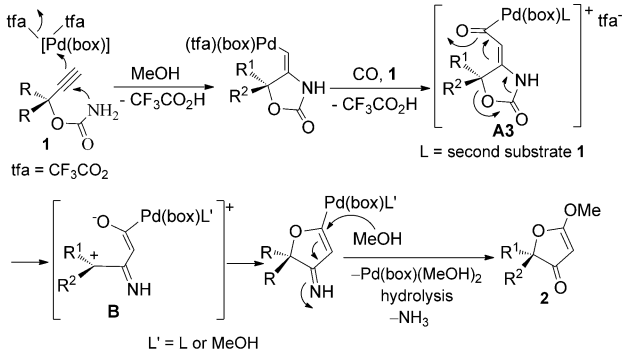
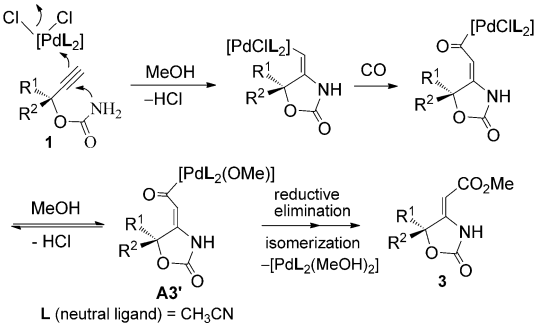


Figure 2. Reaction of the steroids **1o–t** with racemic complex [Pd(tfa)$_2$(±)-**L1**]. Substrates (top)and products (bottom) shown. Reaction conditions: [Pd(tfa)$_2$(±)-**L1**] (5 mol%), *p*-bezoquinone (1.5 equiv), CO, MeOH, 45°C, 1–7 h. Yields are those of isolated products.

A plausible mechanism for the reaction of **1** based on the control experiments (Table 2) is shown in Schemes 2 and 3. The triple bond of the substrate coordinates to palladium(II) and undergoes nucleophilic attack by the intramolecular nucleophilic nitrogen atom followed by CO insertion to produce the acyl palladium intermediate **A3** (Scheme 2). A rapid decarboxylation may take place to generate zwitterionic intermediate **B**, which then cyclizes and is followed by addition of methanol and subsequent hydrolysis of the imine moiety, thus producing the 5-methoxy-3(2*H*)-furanone **2**. Based on our earlier results with similar substrates



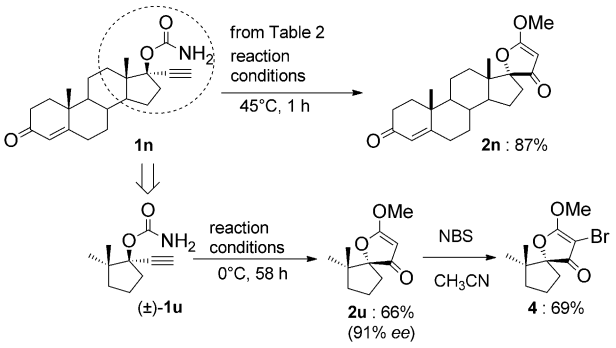
Scheme 2. Plausible reaction mechanism (in the presence of box ligand).



Scheme 3. Plausible reaction mechanism with [(CH$_3$CN)$_2$PdCl$_2$] (in the absence of box ligand).

(Scheme 1 a),[5,6] the box ligand promotes coordination of the second substrate (L) to the acyl palladium intermediate **A3**, thus preventing the methanolysis. In addition, the cationic Pd^{II} center in **A3** is more electrophilic and thus stimulates the rapid decarboxylation more than the neutral Pd^{II} center in **A3′** (Schemes 2 and 3). When using [(CH$_3$CN)$_2$PdCl$_2$] (in the absence of box ligand), methanolysis of the acyl palladium intermediate **A3′** (reductive elimination) followed by isomerization provides the ester **3** (Scheme 3).

To confirm the above hypothesis, the first asymmetric reaction of the racemic substrate (±)-**1u** was investigated (Scheme 4). The model substrate (±)-**1u** was designed based



Scheme 4. First asymmetric reaction of racemic substrate (±)-**1u** in the presence of (*R*,*R*)-**L1**. Reaction conditions: (*R*,*R*)-**L1** (7.5 mol %), Pd(tfa)$_2$ (5 mol %), *p*-benzoquinone (1.5 equiv), CO, MeOH.

on the steroid **1n** given the results in entries 1 and 5 of Table 2. The reaction of (±)-**1u** using (*R*,*R*)-**L1** afforded 91% *ee* of **2u** in 66% yield. The absolute stereochemistry of **2u** was determined by X-ray crystallographic analysis after conversion to the corresponding bromide **4**.[7] As expected, nucleophilic attack of the oxygen atom took place from the *re* face, which is consistent with that in the case of **1n**.

In conclusion, we have presented a cyclization/carbonylation/decarboxylation/cyclization sequence of the propargyl carbamates **1** catalyzed by [(box)Pd^{II}] complexes. The 4-methoxy-3(2*H*)-furanones **2** were obtained in moderate to excellent yields. To elucidate the reaction mechanism, the first asymmetric version of this new reaction was achieved. The optically active spirofuranone **2u** was obtained from the racemic carbamate (±)-**1u** through a dynamic kinetic asymmetric transformation.

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