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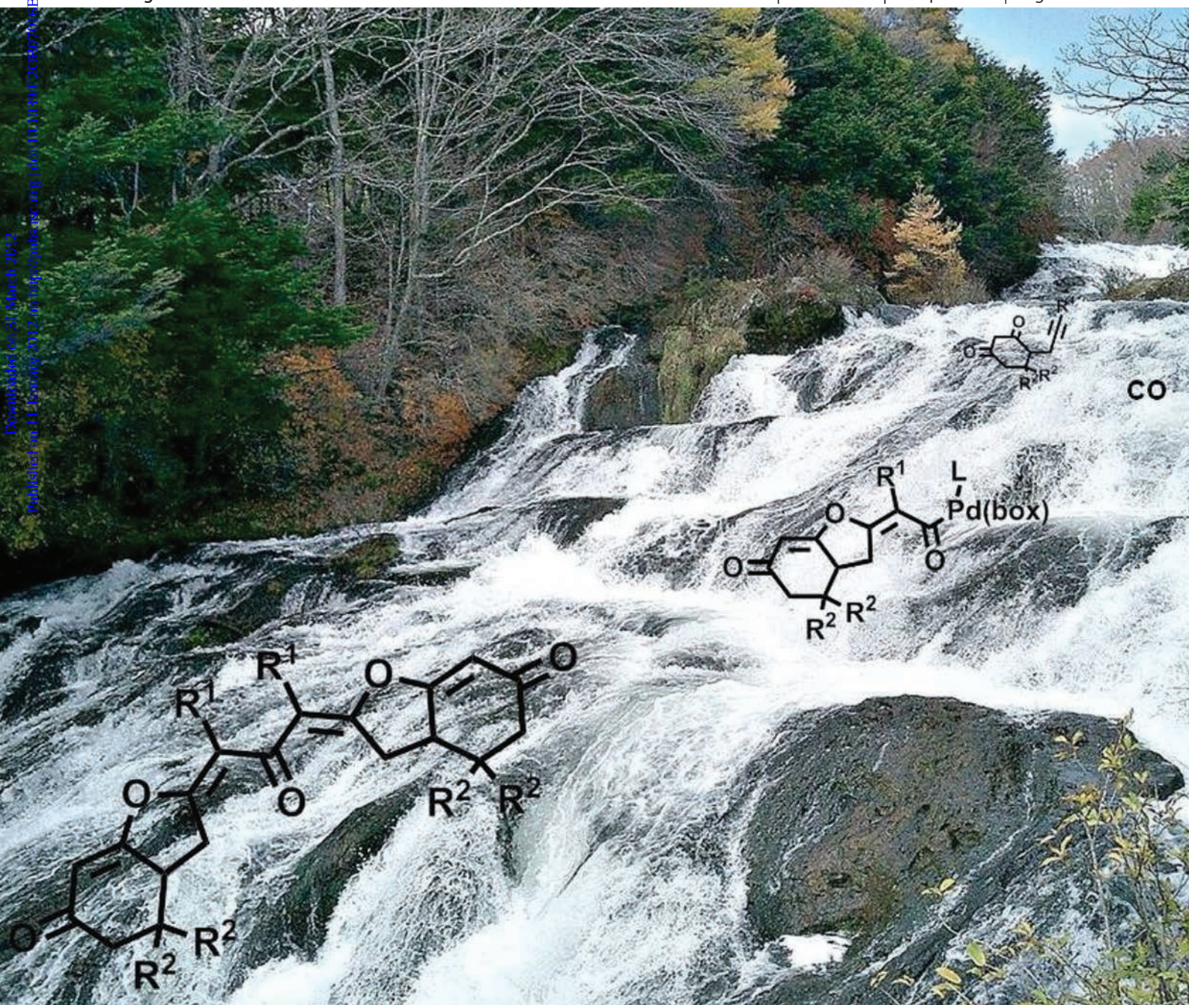

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PAPER

Cyclization–carbonylation–cyclization coupling reaction of γ-propynyl-1,3-diketones with palladium(II)-bisoxazoline catalyst†

Taichi Kusakabe,[a] Yasuko Kawai,[a] Rong Shen,[a] Tomoyuki Mochida[b] and Keisuke Kato*[a]

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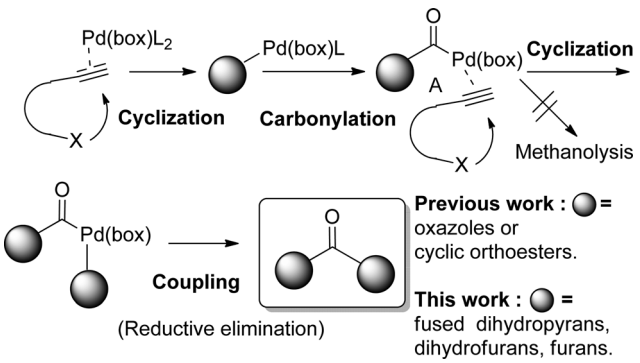
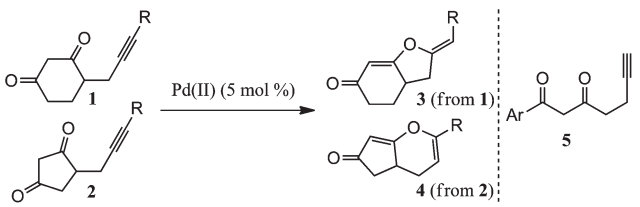
Cyclization–carbonylation–cyclization coupling reaction (CCC-coupling reaction) of γ-propynyl-1,3-diketones catalyzed by (box)Pd^{II} complexes afforded symmetrical ketones bearing two oxabicyclic groups in moderate to excellent yields.

Furan rings are a common structure in a range of biologically active natural products and important pharmaceuticals.[1] Diarylketones are also frequently found in natural products and pharmaceuticals[2] [*e.g.*, suprofen (a non-steroidal anti-inflammatory drug), raloxifene (a selective estrogen receptor modulator – drug for treatment of osteoporosis), benzbromarone (an antipodagric drug), and amiodarone (an antiarrhythmic drug)]. Cascade reactions are important tools for constructing a variety of heterocycles in one step starting from simple compounds.[3] Recently, we reported a cyclization–carbonylation–cyclization coupling reaction (CCC-coupling reaction) of propargylic acetates and amides catalyzed by palladium(II)-bisoxazoline (box) complexes[4a] (Scheme 1). Symmetrical ketones bearing two oxazoles or cyclic orthoesters were obtained in a one-step reaction. In this transformation, the triple bond of the substrate coordinates to palladium(II) and undergoes nucleophilic attack by the intramolecular nucleophile X followed by CO insertion to produce the acyl palladium intermediate **A**. Coordination of the triple bond of a second molecule induces the second cyclization. Reductive elimination then leads to formation of a ketone bearing two heterocyclic groups. We believe that the box ligand enhances the π-electrophilicity of palladium(II),[4] and thus promotes coordination of the second triple bond to the acyl palladium intermediate **A**, leading to dimerization. Previously, Mascareñas *et al.* reported that the palladium(II) catalyzed cyclization of cyclohexanediones **1** and cyclopentanediones **2** afforded oxabicyclic derivatives **3** and **4**, which are important frameworks for the synthesis of prostaglandin derivatives[5a] (Scheme 2). To extend our concept of the CCC-coupling reaction, we planned to investigate the (box)Pd^{II} catalyzed carbonylation reaction of γ-propynyl-1,3-diketones **1**, **2** and **5** (Table 1, Schemes 3–5).



Scheme 1 Our concept of a cyclization–carbonylation–cyclization coupling reaction (CCC-coupling reaction) of propargylic compounds.



Scheme 2 Mascareñas *et al.*: Pd(II) catalyzed cyclization of **1** and **2**.

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 (2 equiv.) in methanol under carbon monoxide atmosphere (balloon) generated the dimeric ketone **6a** in 18% yield along with a mixture of unidentified compounds (Table 1, entry 1). $(Ph_3P)_2PdCl_2$ and $Pd(tfa)_2$ gave a complex mixture (Table 1, entries 2–3). The use of (2,2′-bipyridine)dichloropalladium(II) and (−)-sparteine (**L1**)/$Pd(tfa)_2$, afforded product **6a** in low yields (Table 1, entries 4–5, Fig. 1). Next, an attempt was made to use the box ligand according to our previous results.[4a] As expected, the reaction occurred smoothly in the presence of the box ligands **L2** and **L3**, and the yields improved to 77–83%

[a]*Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba, 274-8510, Japan. E-mail: kkk@phar.toho-u.ac.jp; Fax: +81 474 721 805; Tel: +81 474 721 805*
[b]*Department of Chemistry, Faculty of Sciences, Kobe University, Rokkodai, Nada, Kobe, 657-8501, Japan*

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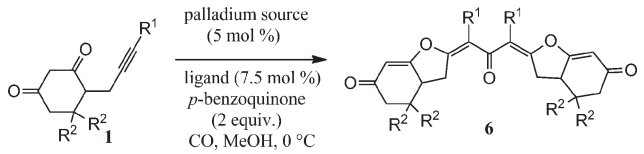
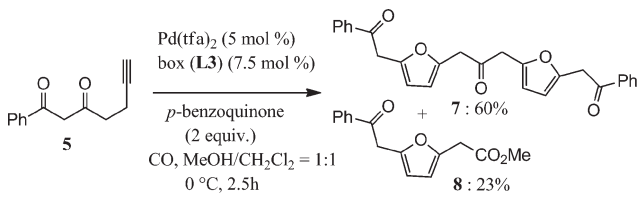
Table 1 CCC-coupling reaction of γ-propynyl-1,3-cyclohexanediones **1**[a]

Entry	R^1	R^2	Palladium source (5 mol%)	Ligand (7.5 mol%)	Time (h)	Yield of **6** (%)
1	H	H	$(CH_3CN)_2PdCl_2$	—	1.5	**6a**: 18
2	H	H	$Pd(tfa)_2$	—	14	Complex mixture
3	H	H	$(Ph_3P)_2PdCl_2$	—	3.0	Complex mixture
4	H	H	(2,2′-bipyridine)$PdCl_2$		14	**6a**: 9
5	H	H	$Pd(tfa)_2$	**L1**	24	**6a**: 16
6	H	H	$Pd(tfa)_2$	box (**L2**)	2.0	**6a**: 77
7	H	H	$Pd(tfa)_2$	box (**L3**)	3.0	**6a**: 83
8	Me	H	$Pd(tfa)_2$	box (**L3**)	2.5	**6b**: 94
9	Et	H	$Pd(tfa)_2$	box (**L3**)	2.0	**6c**: 80
10	*n*Hexyl	H	$Pd(tfa)_2$	box (**L3**)	2.0	**6d**: 86
11[f]	Cyclopropyl	H	$Pd(tfa)_2$	box (**L3**)	53[b]	**6e**: 99
12[f]	Ph	H	$Pd(tfa)_2$	box (**L3**)	6.0	**6f**: 83
13[f]	4-MeOPh	H	$Pd(tfa)_2$	box (**L3**)	39[c]	**6g**: 71
14[f]	4-CF_3Ph	H	$Pd(tfa)_2$	box (**L3**)	12	**6h**: 90
15[f]	4-ClPh	H	$Pd(tfa)_2$	box (**L3**)	11[d]	**6i**: 99
16[f]	Ph	Me	$Pd(tfa)_2$	box (**L3**)	45[e]	**6j**: 81

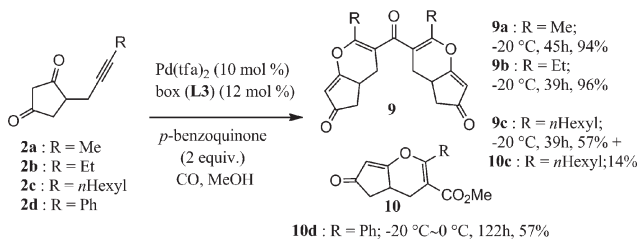
[a] **6a** was obtained as a diasteromeric mixture (ratio = 1.5 : 1–1 : 1). [b] −30 °C. [c] −20 °C. [d] −20 °C ∽0 °C. [e] −20 °C ∽−10 °C. [f] $Pd(tfa)_2$: 10 mol%, **L3**: 12 mol%



Scheme 3 This work: CCC-coupling reaction of γ-propynylcyclohexane-1,3-diones **1** (for Table 1).



Scheme 4 CCC-coupling reaction of acyclic substrate **5**.



Scheme 5 CCC-coupling reaction of γ-propynylcyclopentane-1,3-diones **2**.

(Table 1, entries 6–7). Furthermore, CH_2Cl_2, CH_3CN, DMF and THF were not suitable as solvents.

Having optimized the reaction conditions, we examined the reaction of various internal alkynes **1b**–**j** with the box ligand **L3**. For substrates **1b**–**e** with hydrocarbon substituents (R^1), the reaction proceeded well (80–99% yields) (Table 1, entries 8–11).[6] The aryl-substituted alkynes **1f**–**j** (R^1 = Ar) gave the corresponding dimeric ketones **6f**–**j** in moderate to excellent yields

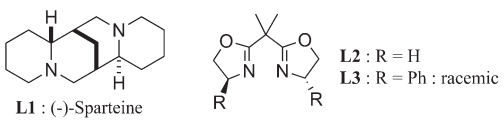


Fig. 1 Ligands for Table 1 (Scheme 3).

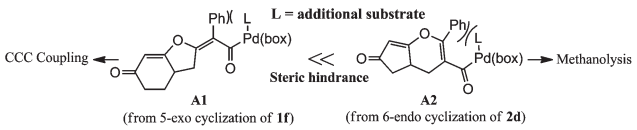


Fig. 2 Comparison of steric hindrance in acyl palladium intermediates **A1** and **A2**.

(Table 1, entries 12–16). A lower yield was obtained for **1g** containing an electron-rich aromatic group as R^1 (Table 1, entry 13). A chlorine atom on the aryl group was tolerated under the reaction conditions (Table 1, entry 15). The reaction of **6j** bearing additional substituents on the cyclohexane ring also proceeded well (Table 1, entry 16).

The scope of the CCC-coupling reaction was then extended to the acyclic substrate **5** and five-membered ring substrates **2** (Schemes 4 and 5). In the case of acyclic substrate **5**, dimeric ketone **7** was obtained in 60% yield along with monomeric ester **8** (23% yield). For five-membered ring substrates **2a** and **2b** with small hydrocarbon substituents (R = Me or Et), the reactions proceeded well (94–96% yields).[6] However, the reaction of **2c** with a large hydrocarbon substituent (R = *n*Hexyl) afforded dimeric ketone **9c** in 57% yield along with monomeric ester **10c** (14% yield). Moreover, the substrate **2d** bearing a phenyl group gave the monomeric ester **10d** exclusively. Although we do not have a clear explanation for the different behavior observed with the six-membered substrate **1f** (R^1 = Ph, R^2 = H, Table 1, entry 12) and five-membered substrate **2d** (R = Ph, Scheme 5) at this stage, we tentatively propose the following (Fig. 2): the acylpalladium intermediates **A1** and **A2** could be produced by the 5-exo cyclization of **1f** and 6-endo cyclization of **2d**, respectively. The

steric hindrance in **A2** inhibited the coordination of the additional substrate to palladium, and thus methanolysis of **A2** proceeded slowly.

In conclusion, we have presented a cyclization–carbonylation–cyclization coupling reaction (CCC-coupling reaction) of γ-propynyl-1,3-diketones **1**, **2** and **5** catalyzed by (box)Pd^{II} complexes. Symmetrical ketones possessing two oxabicyclic groups were obtained in moderate to excellent yields. We believe that the box ligand enhances the π-electrophilicity of palladium(II),[4] and thus promotes coordination of the triple bond (second molecule) to the acyl palladium intermediate **A**, leading to the dimerization reaction. We are currently investigating additional cascade reactions based on the cyclization–carbonylation–cyclization strategy presented here for the synthesis of other types of ketones containing two heterocyclic groups.

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6 The structures of 5-exo cyclization product **6b** and 6-endo cyclization product **9a** were confirmed by HMBC correlations. See the ESI†.

