Palladium-Catalyzed Oxidative Cascade Carbonylative Spirolactonization of Enallenols

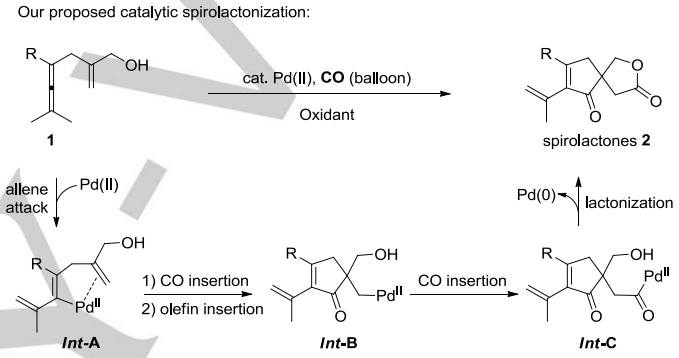
Youai Qiu, Bin Yang, Tuo Jiang, Can Zhu, and Jan-E. Bäckvall*

Abstract: A highly selective palladium-catalyzed oxidative carbonylation-carbocyclization-alkoxycarbonylation of enallenols to afford spirolactones bearing an all-carbon quaternary center has been developed. This transformation involves formation of overall three carbon-carbon (C-C) bonds and one carbon-oxygen (C-O) bond via a cascade insertion of carbon monoxide (CO), olefin, and CO. Preliminary experiments on chiral anion-induced enantioselective carbonylation/carbocyclization of enallenols afforded spirolactones with moderate enantioselectivity.

Following our long-term focus on palladium-catalyzed oxidative carbocyclization of enallenes to construct carbocyclic skeletons,[1-3] we were interested in carrying out the corresponding spirocyclization leading to challenging spirolactones. In particular, we were interested in the synthesis of spirolactones bearing an all-carbon quaternary center by combining palladium-catalyzed oxidative carbocyclization and catalytic carbonylation.[4,5] The latter spirolactone moiety constitutes the core structure of numerous natural alkaloids and pharmaceuticals exhibiting significant biological activities.[6]

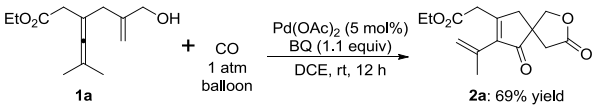
Synthesis of spirocyclic compounds has been considered as a difficult task for a long time. To date, several methods have been developed for the synthesis of spirocycles bearing an all-carbon quaternary center.[7,8] For example, *N*-heterocyclic carbene (NHC)-catalyzed formal [3+2] annulation has been elegantly utilized for the construction of various precious spirocyclic skeletons.[9-11] Furthermore, dearomatization reactions of different aromatic rings[12,13] and alkene metathesis with Grubbs catalysts[14] provide feasible methods for the synthesis of spirocycles. In addition, palladium-catalyzed carbocyclization have also been used to form spirocycles.[15-17] However, less attention has been devoted to the efficient synthesis of spirolactones bearing an all-carbon quaternary center.[18] There is therefore a demand of new synthetic methods that provide access to spirolactones with an all-carbon quaternary center from readily available starting materials.

We set out to investigate whether a Pd^{II}-catalyzed carbonylative spirolactonization of readily available enallenols would constitute a route for synthesis of spirolactones (Scheme 1). Simultaneous coordination of the olefin and allene units of substrate **1** to the Pd^{II} center triggers an allene attack on Pd^{II} via C-H bond cleavage to produce intermediate ***Int*-A**.[19] Then ***Int*-A** may undergo a cascade carbon monoxide (CO) insertion,[4,5] and subsequent carbocyclization[1] via olefin insertion to give ***Int*-B**. The latter intermediate would undergo an additional CO insertion followed by a lactonization, which would provide the desired spirolactone **2**. However, the challenge is how to control the selectivity during the whole process, considering that three carbon-carbon (C-C) bonds and one carbon-oxygen (C-O) bond would be selectively formed in a one-pot cascade reaction.



Scheme 1. Proposed method for formation of spirolactones.

Based on this concept, our initial attempt began with the reaction of enallenol **1a** using 5 mol% of $Pd(OAc)_2$ as catalyst and *p*-benzoquinone (BQ, 1.1 equiv) as the oxidant under 1 atm of CO (balloon). When the reaction was conducted in dichloroethane (DCE) at room temperature for 12 h, the envisaged spirolactone **2a** was obtained in 69% yield (Scheme 2). To our delight, **2a** was the only product observed.



Scheme 2. Initial attempt.

With these inspiring results in hand, we began to optimize the reaction conditions (Table 1). Catalyst screening showed that 1,2-bis(phenylsulfinyl)-ethane·$Pd(OAc)_2$ produced the corresponding spirocyclic compound **2a** in a higher yield (76%) compared to that of $Pd(TFA)_2$ or $Pd(PPh_3)_2Cl_2$ (Table 1, entries 2-4), which indicates that a stabilizing ligand on palladium plays a crucial role for the carbonylative carbocyclization. We therefore investigated the effect of sulfoxide ligands as the additive. Interestingly, addition of 20 mol% of DMSO had a beneficial effect on the reaction, and the yield increased to 84% (entry 5). Solvent screening (entries 6-10) showed that 1,4-dioxane is the best solvent, in which the yield of **2a** was 88% (entry 10). An increased amount of BQ to 1.3 equiv decreased

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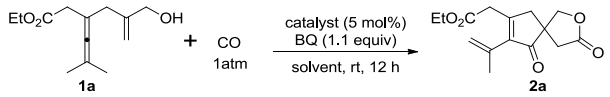
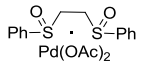
the yield of **2a** to 76% (entry 11). The use of 2,6-dimethyl-BQ in place of BQ gave only 36% yield (entry 12).

Table 1. Optimizing the reaction conditions.[a]

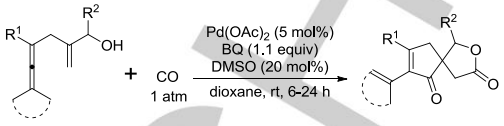


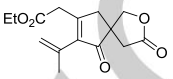
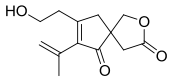
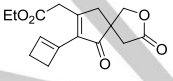
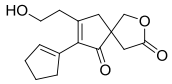
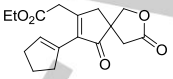
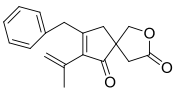
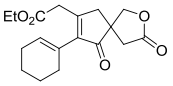
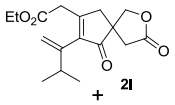
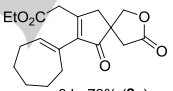
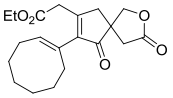
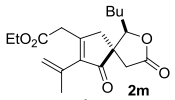
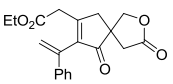
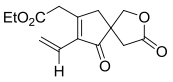
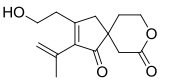
Entry	Catalyst	Solvent	Yield of **2a** [%][b]	Recovery of **1a** [%][b]
1	$Pd(OAc)_2$	DCE	69	-
2	$Pd(TFA)_2$	DCE	61	-
3	$Pd(PPh_3)_2Cl_2$	DCE	55	-
4		DCE	76	-
5[c]	$Pd(OAc)_2$	DCE	84	-
6[c]	$Pd(OAc)_2$	toluene	68	-
7[c]	$Pd(OAc)_2$	THF	38	-
8[c]	$Pd(OAc)_2$	acetone	23	33
9[c]	$Pd(OAc)_2$	MeCN	56	16
10[c]	**$Pd(OAc)_2$**	**dioxane**	**88**	**-**
11[c,d]	$Pd(OAc)_2$	dioxane	76	-
12[c,e]	$Pd(OAc)_2$	dioxane	36	33

[a] The reaction was conducted with 0.2 mmol of **1a** and 5 mol% of catalyst in 2 mL of solvent at rt. [b] Determined by ^{1}H NMR using anisole as the internal standard. [c] DMSO (20 mol%) was used as additive. [d] BQ (1.3 equiv) was used. [e] 2,6-Dimethyl-BQ was used instead of BQ.

Next the substrate scope for the formation of spirolactones **2** was studied under the optimized reaction conditions (Table 2). In addition to methyl substituents on the enallenol moiety (Table 2, entry 1), cyclobutylidene, cyclopentylidene, and cyclohexylidene enallenols (**1b**, **1c**, and **1d**) also afforded the corresponding products **2b**, **2c**, and **2d,** respectively, in good yields (Table 2, entries 2-4). Even medium-sized rings (**1e** or **1f**) gave good yields (entries 5-6). Notably, a high yield (85%) was obtained with methyl- and phenyl-substituted allene (**1g**, entry 7). Monomethyl-substituted enallenol **1h** also underwent the carbocyclization and afforded product **2h** in moderate yield (entry 8). To our delight, enallenols with a free hydroxyl group as in **1i** and **1j**, furnished spirocycles **2i** and **2j** in 81% and 84 % yield, respectively (entries 9 and 10). Furthermore, a benzyl group (**1k**) on the enallenol unit (R^1) was tolerated (entry 11). The reaction of a dissymmetric enallenol **1l** bearing Me and *i*-Pr, afforded **2l** and **2l'** in 75% yield (entry 12). The ratio of **2l** and **2l'** was 1:2 due to the selective allenic C-H bond cleavage, which occurred during allene attack. It is worth noting that R^2 could be *n*-Bu in enallenol **1m**, which afforded product **2m** and **2m'** (dr = 2.2:1) in 68% yield (Table 2, entry 13). However, only a complex mixture was obtained with enallenol **1n** under the standard conditions. To demonstrate the synthetic utility of the current method, the reaction of enallenol **1a** was conducted on a one-gram scale under the standard conditions. Reaction on a 4.5 mmol scale with **1a** afforded 1.076 g (86% yield) of the corresponding spirocyclic compound **2a**.

Table 2. Substrate scope in the palladium-catalyzed carbonylation-carbocyclization-alkoxycarbonylation of enallenols **1**.[a]



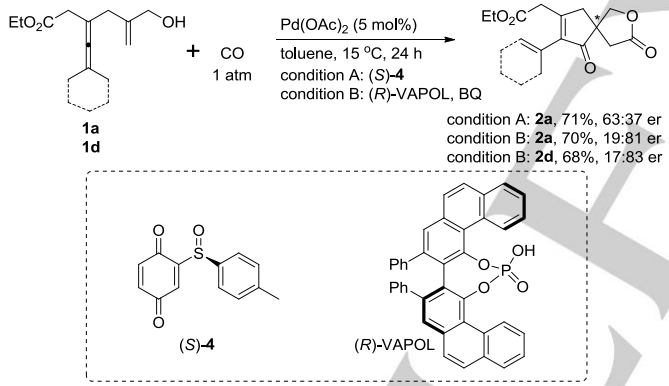
Entry	Product (**2**)[b]	Entry	Product (**2**)[b]
1	 6 h, 85% (**2a**)	9	 15 h, 81% (**2i**)
2	 12 h, 69% (**2b**)	10	 15 h, 84% (**2j**)
3	 8 h, 72% (**2c**)	11	 8 h, 75% (**2k**)
4	 8 h, 80% (**2d**)	12	 **2l** + **2l`** 15 h, 75% (**2l**:**2l`** = 1:2)
5	 8 h, 73% (**2e**)		
6	 8 h, 81% (**2f**)	13	 **2m** + **2m'** 8 h, 68% (**2m**:**2m'** = 2.2 :1)
7	 12 h, 85% (**2g**)		
8[c]	 24 h, 22% (**2h**)	14[d]	 15 h, - (**2n**)

[a] The reaction was conducted with enallenol **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), BQ (1.1 equiv), and DMSO (20 mol%) in 1,4-dioxane at rt. [b] Isolated yield. [c] The reaction was conducted at 60 ^{o}C. [d] Complex mixture.

We further studied the intramolecular hydroalkoxylation reaction of spirolactone **2j**. The reaction with 1.2 equivalents of $BF_3{\cdot}OEt_2$ furnished the corresponding bis-spirocyclic compound **3j** in 90% yield in a single-step, which is an important structural scaffold in biologically active skeletons and natural products.[7]

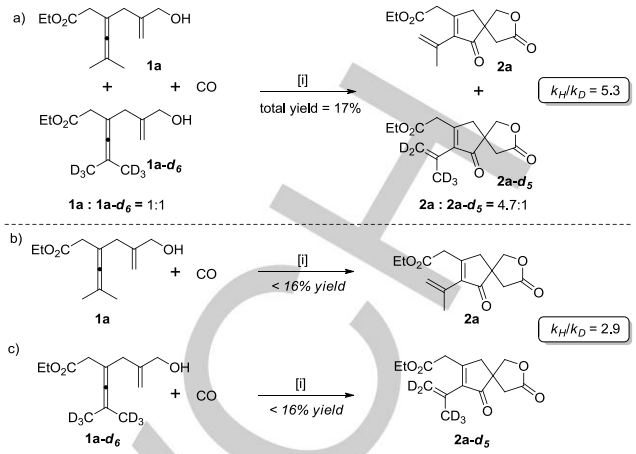
Scheme 3. Transformation of **2j**.

After realization of the racemic construction of spirolactones via the palladium-catalyzed cascade reaction of enallenols, we next carried out preliminary studies on the enantioselective version (Scheme 4), which may provide enantiomerically enriched spiroheterocycles. The latter compounds are widely embedded in various natural products. Interestingly, we found that when chiral BQ (*S*)-**4** was used in place of BQ, **1a** afforded **2a** with a moderate er value (63:37), which implies that the quinone coordinates to Pd in the step in which the chiral center is formed. To our delight, a comparatively good er value (19:81) was achieved in the palladium-catalyzed spirolactonization when (*R*)-VAPOL phosphoric acid (10 mol%) was used as co-catalyst.[20-22] In addition, a slightly higher er value (17:83) was observed with enallenol **1d**, which incorporated a cyclohexylidene enallenol moiety. Because of the high acidity of the phosphoric acid it will protonate off the acetate on Pd^{II} and the phosphate anion will replace the acetate.[21a] In this way the chiral phosphate will induce enantioselectivity in the cyclization to form ***Int*-B** (Scheme 1).



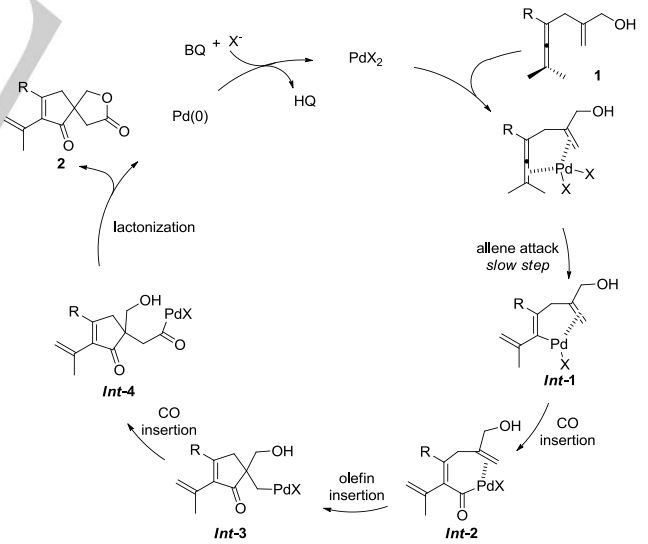
Scheme 4. Preliminary results of the asymmetric reactions.

To gain further insight into the mechanism of this cascade reaction, the deuterium kinetic isotope effects were studied (Scheme 5).[23] An intermolecular competition experiment was conducted using a 1:1 mixture of **1a** and **1a-*d*$_6$** at room temperature for 30 min (Scheme 5a). The product ratio **2a**/**2a-*d*$_5$** measured (ca. 18% conv.) was 4.7:1, and the total yield of **2a**/**2a-*d*$_5$** was 17%. From this ratio, the competitive KIE was determined to k_H/k_D = 5.3. Furthermore, parallel kinetic experiments afforded a KIE (k_H/k_D from initial rate) value of 2.9 (Scheme 5b and 5c). These results indicate that the initial allenic C-H bond cleavage is partially rate-limiting. The large competitive isotope effect in the C-H bond cleavage (k_H/k_D = 5.3) requires that this step is the first irreversible step.



Scheme 5. Kinetic isotope effect studies. [i] Reaction conditions: allene **1a** (or **1a-*d*$_6$**) (0.2 mmol), $Pd(OAc)_2$ (5 mol%), BQ (1.1 equiv), and DMSO (20 mol%) in 1,4-dioxane under CO (1 atm) at rt.

Based on the reaction outcome and the KIE studies, a possible mechanism for this cascade reaction is proposed in Scheme 6. Coordination of the allene and the olefin units to the Pd(II) center would trigger formation of vinylpalladium intermediate ***Int*-1** via allene attack on Pd involving allenic C-H bond cleavage.[19] Insertion of CO into the C-Pd bond of ***Int*-1** would form intermediate ***Int*-2**. Subsequent olefin and CO insertion would give intermediate ***Int*-4** via ***Int*-3**. Finally, intramolecular reaction of ***Int*-4** with the hydroxyl group provides the spirolactone **2**.



Scheme 6. Proposed mechanism.

In conclusion, we have developed a palladium-catalyzed oxidative carbonylation-carbocyclization-alkoxycarbonylation of enallenols in a cascade for the selective formation of spirolactones bearing an all-carbon quaternary center. The reaction is highly chemoselective and involves formation of overall three C-

C bonds and one C-O bond. Mechanistic studies indicate that the allenic C-H bond cleavage is a partially rate-limiting step. Preliminary studies on the enantioselective version of the reaction were attempted, where VAPOL phosphoric acid served as a co-catalyst for the enantioselective carbonylation/carbocyclization/alkoxycarbonylation. Finally, because of the highly efficient construction of spirocycles, especially those bearing an all-carbon quaternary center, the reaction developed here should be useful in synthetic and pharmaceutical chemistry.

Acknowledgements

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Keywords: spirolactones • palladium • oxidation • enallenol • carbocyclization

[1] For selected examples involving palladium-catalyzed oxidative carbocyclization of allenes, see: a) A. K. Å. Persson, J.-E. Bäckvall, *Angew. Chem. Int. Ed.* **2010**, *49*, 4624; *Angew. Chem*. **2010**, *122*, 4728; b) A. K. Å. Persson, T. Jiang, M. Johnson, J.-E. Bäckvall, *Angew. Chem. Int. Ed.* **2011**, *50*, 6155; *Angew. Chem*. **2011**, *123*, 6279; c) Y. Deng, T. Bartholomeyzik, A. K. Å. Persson, J. Sun, J.-E. Bäckvall, *Angew. Chem. Int. Ed*. **2012**, *51*, 2703; *Angew. Chem*. **2012**, *124*, 2757.

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[23] For details of kinetic isotope effect study, see the Supporting Information.

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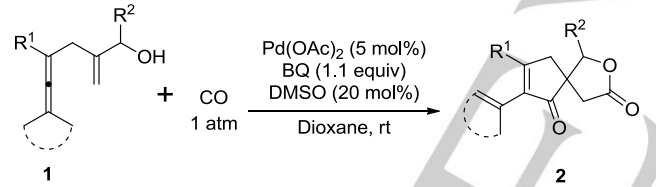

Highly selective cascade C-C/C-O bond formation via palladium-catalyzed oxidative carbonylation-carbocyclization-alkoxycarbonylation of enallenols has been developed, affording spirolactones bearing an all-carbon quaternary center. Preliminary attempts to obtain enantioselectivity in the carbonylative carbocyclization revealed that the VAPOL-type chiral phosphoric acid served as a good anionic co-catalyst in this transformation.

*Youai Qiu, Bin Yang, Tuo Jiang, Can Zhu, and Jan-E. Bäckvall**

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