

An Efficient Synthesis of 2,5-Dihydrofuran-Fused Bicyclic Skeletons via the Pd(II)-Catalyzed Tandem-Cyclization Reaction of 1, ω -Bisallenols

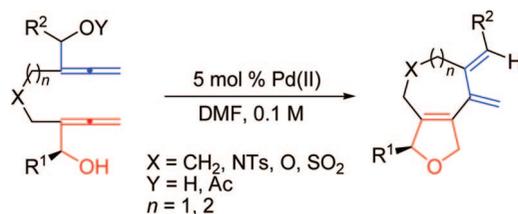
Youqian Deng, Yunlong Shi, and Shengming Ma*

Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, Zhejiang, People's Republic of China

masm@mail.sioc.ac.cn

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ABSTRACT



A palladium(II)-catalyzed tandem double-cyclization reaction of 1, ω -bisallenols was developed to form 2,5-dihydrofuran-fused bicyclic skeletons. With “unsymmetric” substrates, the reaction may also be realized with one hydroxyl group being protected as the acetate. Optically active bicyclic products were prepared by applying the Novozym-435 catalyzed kinetic resolution and the tandem double cyclization of these optically active allenol-allenyl acetates. The reaction may proceed via an oxypalladation, insertion, and elimination process.

Fused bicyclic skeletons are a class of most commonly observed structural units in natural products¹ and unnatural products with biological potential.² As we know, 2,5-dihydrofurans also widely exist in biologically active compounds;³ thus, many new methods have been developed for the efficient synthesis of 2,5-dihydrofurans.⁴ Alcaide et al.

reported the cyclization of 2,3-allenols in the presence of 2,3-allenyl acetates.⁵ In the same year, Hashmi et al. reported that the AuCl₃-catalyzed cyclization of tertiary 2,3-allenols yielded a mixture of cycloisomerization products, double cyclization products, and other products.⁶ Recently, on the

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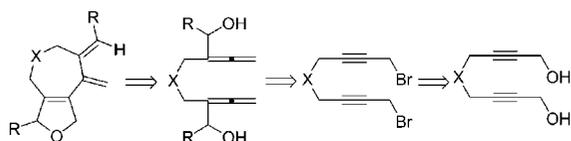
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basis of our previous studies on the cyclization of 2,3-allenoic acids in the presence of 2,3-allenols,⁷ we have developed the cyclization of one 2,3-allenol in the presence of another⁸ or the same⁹ 2,3-allenol, affording 4-(1',3'-dien-2'-yl)-2,5-dihydrofuran via an oxypalladation–carbopalladation– β -hydroxide elimination mechanism. In this paper, we report an efficient and controlled double cyclization approach to the synthesis of 2,5-dihydrofuran-fused bicyclic skeletons from the readily available bis(2,3-allenols) or 2,3-allenol-allenyl acetates, in which even the eight-membered rings were formed easily (Scheme 1).

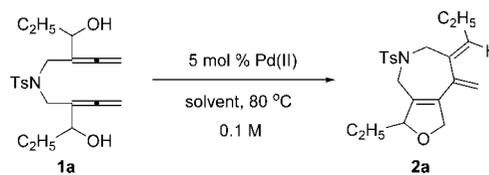
Scheme 1



Our efforts in this area started with the reaction of N-tethered bisallenol **1a** under the catalysis of 5 mol % PdI₂ in CH₂Cl₂, affording the fused bicyclo[5.3.0]product **2a** in 23% yield with 59% of **1a** being recovered (Table 1, entry 1). The reaction in other solvents, such as CH₃NO₂, CH₃CN, CH₃CO₂C₂H₅, THF, DMPU, DMSO, or DMA, also yielded **2a** (Table 1, entries 2–8), different from what was observed in the intermolecular reaction.⁹ There is a solvent effect here: the reaction in DMA is low-yielding (Table 1, entry 8), and the best result was obtained when the reaction was conducted in DMF (Table 1, entry 9). Among different Pd(II) catalysts, PdCl₂ is the best (Table 1, entries 9–15). The reaction of **1a** may also proceed at rt to give **2a** in the same yield with a longer reaction time (Table 1, entry 12).

With the optimized reaction conditions in hand, further investigation for the scope of the reaction of symmetric substrates was conducted with the different R substituents and tether “X” (Table 2). The bisallenols **1a** and **1b** with NTs as the tether provided the bicyclo[5.3.0]products **2a** and **2b** in 62% and 78% yields, respectively (Table 2, entries 1 and 2) under the catalysis of 5 mol % PdCl₂ at 25 °C (conditions A). However, no expected product was formed under conditions A from bisallenol **1c** with a carbon tether (Table 2, entry 3). Fortunately, when 0.5 equiv of NaI was applied as the additive, the reaction afforded **2c** in 58% yield; however, again the reaction should be carried out in DMF instead of DMA⁹ to ensure a good yield (entry 4 in Table 2, defined as conditions B). The α -aryl-substituted bisallenol **1d** can afford the product **2d** in 51% yield under conditions B (Table 2, entry 5). The bisallenols **1e**, **1f**, and **1g** with the ether functional group as the tether may also provide the fused bicyclo[5.3.0]products

Table 1. Effects of Solvent and Catalyst on the Pd(II)-Catalyzed Tandem-Cyclization Reaction of Bis(2,3-allenol) (**1a**)



entry	solvent	Pd(II) (5 mol %)	time (h)	yield of 2a ^a (%)	recovery of 1a (%)
1	CH ₂ Cl ₂	PdI ₂	1.5	23	59
2	CH ₃ NO ₂	PdI ₂	2	0	81
3	CH ₃ CN	PdI ₂	1.5	18	0
4	AcOEt	PdI ₂	1.5	32	0
5	THF	PdI ₂	1.5	36	0
6	DMPU	PdI ₂	2	0	29
7	DMSO	PdI ₂	1	45	0
8	DMA	PdI ₂	1	45	0
9	DMF	PdI ₂	1	66	0
10	DMF	PdBr ₂	1	57	0
11	DMF	PdCl ₂	1	70	0
12 ^b	DMF	PdCl ₂	4	68	0
13	DMF	PdCl ₂ (PhCN) ₂	1	61	0
14	DMF	Pd(OAc) ₂	1	0	89
15	DMF	PdCl ₂ (PPh ₃) ₂	1	0	97

^a Determined by ¹H NMR analysis using 1,3,5-trimethylbenzene as the internal standard. ^b The reaction was conducted at 25 °C.

2e, **2f**, and **2g** smoothly in 57%, 67%, and 65% yields, respectively, under conditions B (Table 2, entries 6–8). The reaction may also be catalyzed by applying 5 mol % PdI₂ at 25 °C (Table 2, entry 9). The sulfone tether may also be used (Table 2, entry 10). In addition, by applying this protocol, even the bicyclo[6.3.0]products **2i** and **2j** can be formed in 68% and 75% yields, respectively, although the formation of the eight-membered ring is always not easy (Table 2, entries 11 and 12).^{10–12} It is important to note that the C=C bond in the products is in the *E*-form, which was established by the NOESY analysis of **2e**. ¹H NMR spectra of the crude product indicated the formation of only one stereoisomer, which is very different from what was observed in the intermolecular reaction.⁹

Unfortunately, when an “unsymmetric” 1,6-bisallenol **1k** was used, as expected the reaction afforded a mixture of

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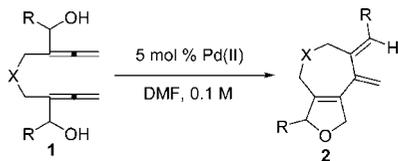
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Table 2. Pd(II)-Catalyzed Coupling-Cyclization Reaction of 1,5-Bisallenols **1**^a

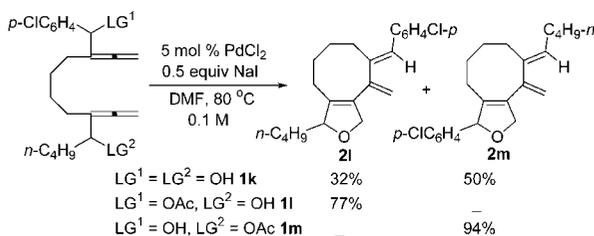


entry	X	R	conditions/time (h)	yield of 2 (%)
1	NTs	C ₂ H ₅ (1a)	A/4	62 (2a)
2	NTs	<i>n</i> -C ₆ H ₁₁ (1b)	A/4	78 (2b)
3	CH ₂	C ₂ H ₅ (1c)	A/4	0 (2c)
4	CH ₂	C ₂ H ₅ (1c)	B/1	58 (2c)
5	CH ₂	<i>p</i> -ClC ₆ H ₄ (1d)	B/1	51 (2d)
6	O	C ₂ H ₅ (1e)	B/2	57 (2e)
7	O	<i>i</i> -C ₃ H ₇ (1f)	B/2	67 (2f)
8	O	<i>n</i> -C ₄ H ₉ (1g)	B/1	65 (2g)
9	O	<i>n</i> -C ₄ H ₉ (1g)	4 ^b	69 (2g)
10	SO ₂	C ₂ H ₅ (1h)	B/1	81 (2h)
11	(CH ₂) ₂	<i>n</i> -C ₄ H ₉ (1i)	B/1	68 (2i)
12	(CH ₂) ₂	<i>p</i> -ClC ₆ H ₄ (1j)	B/1	75 (2j)

^a Conditions A: 5 mol % PdCl₂ was used as the catalyst at 25 °C; Conditions B: 5 mol % PdCl₂ and 0.5 equiv of NaI were used as the catalyst at 80 °C. ^b 5 mol % PdI₂ was used as the catalyst at 25 °C.

inseparable eight-membered products **2l** and **2m** in 32% and 50% yields, respectively. However, if one of the hydroxyl groups was protected, i.e., allenol-allenyl acetates **1l** and **1m**,⁵ the reaction afforded the products **2l** and **2m** in 77% and 94% yields, respectively (Scheme 2).

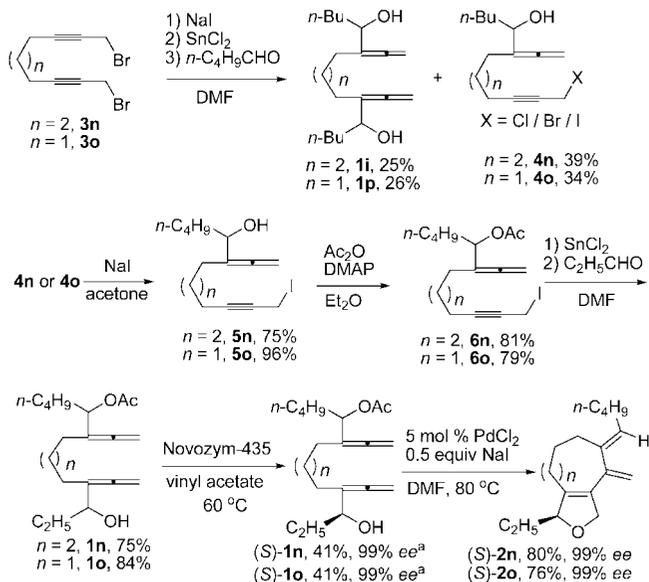
Scheme 2



In addition, to prepare highly optically active substrates, the bis-propargyl bromides **3n** or **3o** were reacted with aldehydes in the presence of NaI and SnCl₂¹³ to afford propargyl halide-allenols **4n** or **4o** together with the corresponding bisallenols **1i** or **1p**. During this reaction the bromides were converted to a mixture of chlorides, bromides, and iodides, which were transformed into the related iodides **5n** or **5o** by the reaction with NaI in acetone. Subsequently, the free hydroxyl group was protected as acetate to afford propargyl halide-allenyl acetates **6n** or **6o**. The propargyl halide moiety in **6n** or **6o** was converted to allenol to yield the racemic allenol-allenyl acetates **1n** or **1o**, which were kinetically resolved using Novozym-435, a protocol developed in this group,¹⁴ to afford the optically active starting

2,3-allenol-allenyl acetates (*S*)-**1n** (99% ee) and (*S*)-**1o** (99% ee). Their reactions under standard reaction conditions B afforded the optically active fused bicyclic products (*S*)-**2n** in 80% yield and 99% ee and (*S*)-**2o** in 76% yield and 99% ee, respectively (Scheme 3) without obvious racemization.

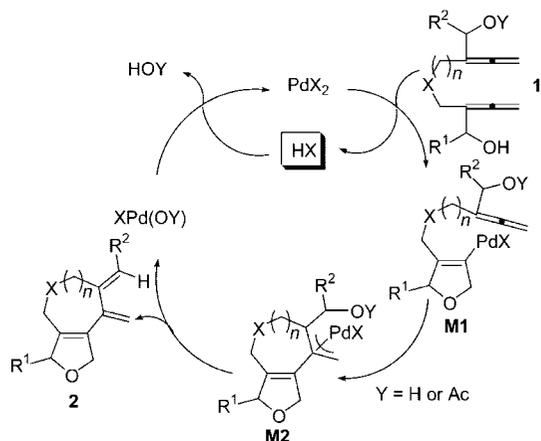
Scheme 3. Synthesis and Cyclization of Optically Active Substrates (*S*)-**1n** and (*S*)-**1o**



^a Referred to the resolved allenol part.

The formation of 2,5-dihydrofuran-fused bicyclic skeletons can be rationalized by the mechanism shown in Scheme 4. First, the cyclic oxypalladation of the 2,3-allenol moiety in **1** with Pd(II) would form intermediate **M1**. Then regioselective intramolecular carbopalladation of the remaining allene unit in **M1** would form the π -allylic palladium intermediate **M2**. Subsequent trans- β -hydroxide^{7–9,15} or acetate^{5,16} elimination would afford product **2** highly stereoselectively (Scheme 4).

Scheme 4. Possible Mechanism of the Coupling-Cyclization Reaction of 1,5-Bisallenols **1**



In conclusion, we have developed a palladium(II)-catalyzed tandem double-cyclization reaction of 1, ω -bisallenols to form 2,5-dihydrofuran-fused bicyclic skeletons from the readily available bis(2,3-allenols). With “unsymmetric” substrates, the reaction may be realized by converting one hydroxyl group to acetate. Optically active bicyclic products may be easily prepared by applying the Novozym-435 catalyzed kinetic resolution and the tandem double cycliza-

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tion of these optically active substrates. Because of the importance of fused bicyclic skeletons and 2,5-dihydrofurans, this method would be potentially useful in organic chemistry and medicinal chemistry. Further studies in this area are being pursued in our laboratory.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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