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Palladium-Catalyzed Cyclization Reaction of Allylic Bromides with 1,2-Dienyl Ketones. An Efficient Synthesis of 3-Allylic Polysubstituted Furans

Shengming Ma* and Lintao Li

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P.R.China

masm@pub.sioc.ac.cn

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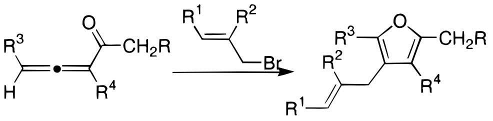
ABSTRACT



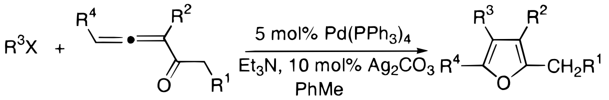
Conditions: 5 mol% PdCl$_2$(PhCN)$_2$, K$_2$CO$_3$, CH$_3$CN, 25 °C

3-Allylic polysubstituted furans were synthesized via a palladium-catalyzed cyclization reaction of allylic bromides with differently substituted 1,2-allenyl ketones. This process may occur via the reaction of a furanyl palladium intermediate with allylic bromide.

Furans, one of the most commonly studied heterocyclic compounds,[1,2] can be, in principle, synthesized from either cyclization of acyclic precursors or derivatization of the furan rings.[3,4] In the latter case, usually the introduction of substituents at the 2- or 5-position is relatively easy, while a similar operation at the 3- or 4-position is difficult. Thus, one of the most pursued entries to polysubstituted furans is the cyclization reaction of acyclic precursors since different substituents can be preloaded at the desired locations in the starting materials.[5,6] Thus, the substituent-incorporation capability of the starting materials will be the key point for the efficiency of the related methodology.

Properly polysubstituted allenes are a class of such interesting compounds, which offer both the capability of having as many as four substituents and chirality. Among our efforts in the area of allene chemistry,[7] we have recently demonstrated an efficient synthetic route to polysubstituted furans via the Pd(0)-catalyzed cyclization reaction of aryl halides or 3-iodo-2-propenoate with 1,2-allenyl ketones (Scheme 1).[8]

Scheme 1



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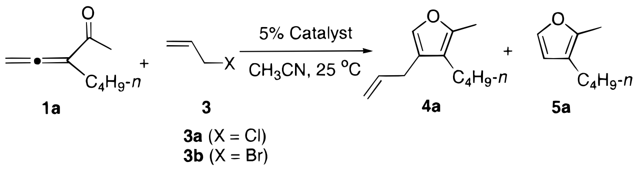
10.1021/ol0055871 CCC: $19.00

Table 1. Reaction of 3-Butyl-3,4-pentadien-2-one with Allyl Chloride or Bromide[a]



entry	**3**	ratio of **1a**/**3**	catalyst	time (h)	base	**4a** + **5a** (%)[b]	ratio of **4a/5a**[e]
1	**3a**	1/3	$Pd(OAc)_2$	24	Et_3N	13	38/62
2	**3a**	1/3	$Pd(OAc)_2/Ag_2CO_3$	24	K_2CO_3	37	89/11
3	**3b**	1.5/1	$Pd(PPh_3)_4/Ag_2CO_3$	18	Et_3N	40[c,d]	5/95
4	**3b**	1.5/1	$Pd(OAc)_2/Ag_2CO_3$	29	K_2CO_3	81[c]	96/4
5	**3b**	1/1.2	$Pd(OAc)_2/Ag_2CO_3$	20	K_2CO_3	62	92/8
6	**3b**	1/2	$PdCl_2/Ag_2CO_3$	21	K_2CO_3	45	98/2
7	**3b**	1/2	$PdCl_2(CH_3CN)_2/Ag_2CO_3$	20	K_2CO_3	62	99/1
8	**3b**	1/2	$PdCl_2(PhCN)_2/Ag_2CO_3$	17	K_2CO_3	71	99/1
9	**3b**	1/2	$PdCl_2(CH_3CN)_2$	20	K_2CO_3	61	99/1
10	**3b**	1/2	$PdCl_2(PhCN)_2$	21	K_2CO_3	*72*	*99/1*
11	**3a**	1/3	$Pd(OAc)_2$	24	K_2CO_3	46	84/16
12	**3b**	1/2	$PdCl_2(PhCN)_2$	21	none	*18*	96/4
13	**3a**	1/3	$Pd(OAc)_2$	21	none	10	82/18

[a] The reaction was carried out at rt using **1a** (1 mmol), **3** (see the above table for the amount used), catalyst (5 mol %), and base (1 mmol) in MeCN (2 mL). [b] Isolated yield based on **1a**. [c] Isolated yield based on **3b**. [d] The reaction was carried out at 100 °C using **1a** (1.5 mmol), **3b** (1 mmol), $Pd(PPh_3)_4$ (5 mol %), Ag_2CO_3 (10 mol %), and Et_3N (2 mmol) in toulene (4 mL). [e] Determined by ^1H NMR analysis.

However, one disadvantage of this methodology is that R^3 could not be an alkyl group because of the intrinsic difficulty of the oxidative addition reaction of Pd(0) with alkyl halides as well as the potential β-H elimination reaction of the alkyl palladium species. Thus, continuing our efforts toward the tool box for the synthesis of polysubstituted furans, we addressed our attention to the use of allylic halides[9] in order to obtain the R^3 = allyl-type polysubstituted furans. In that case, functionalization of the allylic double bond would provide access to a new class of polysubstituted furans. However, the corresponding reaction failed to afford the R^3 = allyl-type polysubstituted furans in decent yield under the conditions described in ref 8 (entry 3, Table 1). Thus, we designed a Pd(II)-based catalytic route for this conversion, which may occur via the interaction of the furanyl palladium species **2** with allyl bromide[9a,b] (Scheme 2).

We studied the Pd(II)-catalyzed cyclization of 3-butyl-3,4-pentadien-2-one and allyl bromide or chloride. The results are summarized in Table 1. Under the catalysis of $Pd(OAc)_2$ or $Pd(OAc)_2-Ag_2CO_3$, the reaction afforded a mixture of the expected cyclization-coupling product **4a** and

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(6) For Rh^+- or Ag^+-catalyzed direct one-component cyclization of 1,2-dienyl ketones to afford up to trisubstituted furans, see: Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450−3451. Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 960−969. Marshall, J. A.; Wallace, E. M. *J. Org. Chem.* **1995**, *60*, 796−797. Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169−7171.

(7) (a) For the Pd(0)/Ag^+-cocatalyzed cyclization of organic halides with 1,2-allenyl carboxylic acids to afford butenolides, see: Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387−6389. (b) For cyclization of 1,2-allenyl carboxylic acids to afford β-halobutenolides, see: Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett.* **1999**, *40*, 2393−2396. Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, *55*, 12137−12148. Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314−9317. (c) For the corresponding reaction of 2,3-dienols with organic halides to afford oxiranes, see: Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943−7944.

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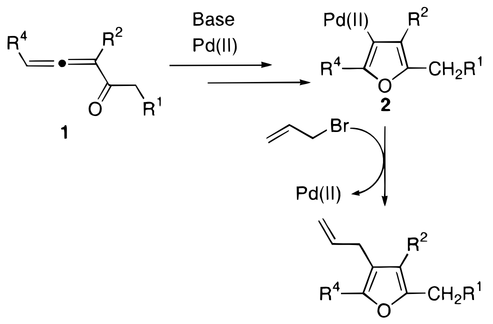
(9) For the Pd-catalyzed allylation−cyclization reactions see: (a) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655−3661. (b) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Bazaki, H. *J. Org. Chem.* **1991**, *56*, 5816−5819. (c) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1992**, *57*, 6377−6379.

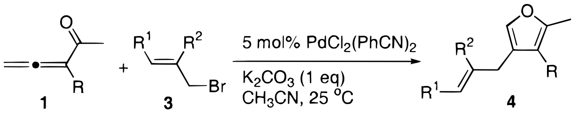
Scheme 2



cycloisomerization product **5a**[6,8,10] with from poor to good yields and selectivities. The reaction afforded **4a** in good yield with a **4a**/**5a** selectivity of as high as 99:1 under the catalysis of $PdCl_2(RCN)_2-Ag_2CO_3$ (R = Me or Ph) (entries 7 and 8, Table 1). Control experiment showed that addition of Ag_2CO_3 is not necessary (compare entries 8 with 10, Table 1). Usually the yields with $PdCl_2(PhCN)_2$ are higher than those with $PdCl_2(CH_3CN)_2$ (compare entries 7 and 8, 9 and 10, Table 1). However, in the absence of K_2CO_3, the reaction afforded **4a** in very low yield (entries 12 and 13, Table 1).

Some typical results for the Pd(II)-catalyzed cyclization reaction of 1-substituted-1,2-dienyl ketones with differently substituted allylic bromide are summarized in Table 2. The following points should be noted: (1) the yields range from moderate to good; (2) for 3-phenyl-2-propenyl bromide **3d**, the coupling occurs exclusively at the nonsubstituted terminals (entries 2, 4, and 7, Table 2); (3) the configuration of the C=C bond in 3-phenyl-2-propenyl bromide remained intact (entries 2, 4, and 7, Table 2); (4) using 3-allyl-3,4-pentadien-2-one **1c** as the starting material provides extra opportunity for further functionalization upon this allylic carbon−carbon double bond (entries 6−8, Table 2); (5) the reaction of 3-butyl-3,4-pentadien-2-one with 3-phenyl-2-propenyl bromide under the same reaction conditions except that PPh_3 (4 equiv) was added did not occur to afford furan **4c**. In addition, this reaction did not occur using $Pd(PPh_3)_4$ as the catalyst. However, it is interesting to note that the reaction could also be catalyzed by a Pd(0) catalyst, i.e., $Pd_2(dba)_3 \cdot CHCl_3$, to afford **4c** in 79% yield (Scheme 3). A catalytic cycle involving Pd(0) is also proposed (Scheme 4). Here π-allyl palladium species **6** promotes the cyclization to afford π-allyl 3-furanyl palladium species **7**, which gives the final product and regenerates Pd(0) via a higly regioselective coupling reaction.

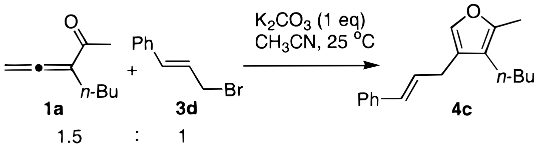
Table 2. Reaction of 1-Substituted 1,2-Allenyl Ketones with Allyl Bromides[a]



entry	1 R	3 R¹	 R²	time (h)	yield of 4[b]
1	*n*-Bu (**1a**)	H	Ph (**3c**)	19	78 (**4b**)
2	*n*-Bu (**1a**)	Ph	H (**3d**)	23	53 (**4c**)
3	Me (**1b**)	H	H (**3b**)	19	62 (**4d**)
4	Me (**1b**)	Ph	H (**3d**)	20	50 (**4e**)
5	Me (**1b**)	H	Ph (**3c**)	20	52 (**4f**)
6	allyl (**1c**)	H	H (**3b**)	21	52 (**4g**)
7	allyl (**1c**)	Ph	H (**3d**)	22	53 (**4h**)
8	allyl (**1c**)	H	Ph (**3c**)	22	70 (**4i**)

[a] The reaction was carried out at rt using **1** (1.5 mmol), **3** (1 mmol), $PdCl_2(PhCN)_2$ (5 mol %), and K_2CO_3 (1 mmol) in MeCN (2 mL). [b] Isolated yield was based on **3**.

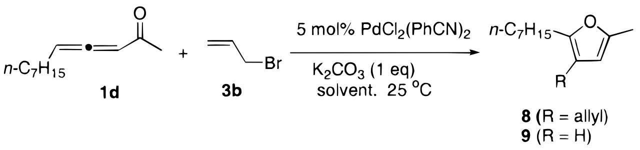
Scheme 3



catalyst (5 mol%)	yield of **4c**
$Pd(PPh_3)_4$	0 %
$PdCl_2(PhCN)_2$, 20 mol%PPh_3	0 %
$Pd_2(dba)_3 \cdot HCCl_3$	79 %

For the cyclization reaction of 3-substituted-1,2-dienyl ketone, i.e., 3,4-dodecadien-2-one **1d**, with allyl bromide, the results in acetonitrile were poor (entry 1, Table 3). Indeed, solvent effect on the selectivity of **8** over **9** was obvious. After some screening the reaction afforded the expected product **8** in DMF in the presence of 10 equiv of allyl bromide in reasonable yield and good selectivity (92:8) (Table 3).

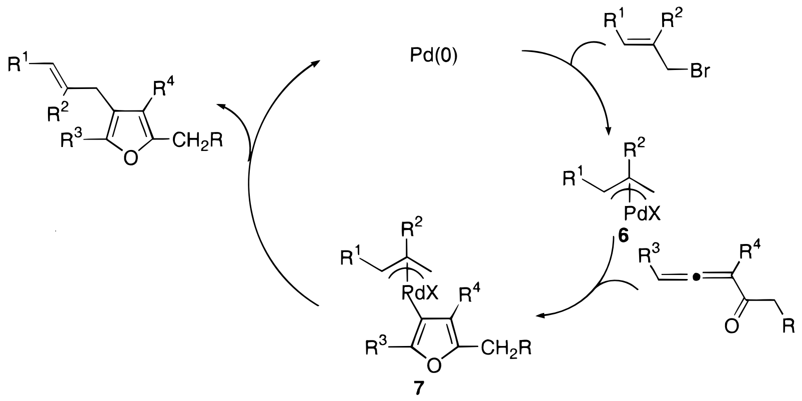
Table 3. Reaction of 3,4-Dodecadien-2-one with Allyl Bromide[a]



entry	molar ratio of **1d**/**3b**	solvent	time (h)	yield of **8** + **9** (%)[b]	ratio of **8**/**9**[c]
1	1/6	CH_3CN	15	58	75/25
2	1/6	DMF	15	67	81/19
3	1/6	toluene	16	66	28/72
4	1/6	THF	16	58	44/56
5	1/10	DMA	22	57	90/10
6	1/20		22	76	51/49
7	1/10	DMF	22	65	92/8

[a] The reaction was carried out at rt using **1d** (1 mmol), **3** (see the above table for the amount used), $PdCl_2(PhCN)_2$ (5 mol %), and K_2CO_3 (1 mmol) in solvent (2 mL). [b] Isolated yield based on **1d**. [c] Determined by ^1H NMR analysis.

Scheme 4



In conclusion, we have developed an efficient entry to 3-allyl polysubstituted furans. Because of its simple operation and easily availability and diversity of both starting materials, this two-component cyclization-coupling protocol will provide an efficient access to a variety of polysubstituted furans. The study on the scope, synthetic application, and mechanism of this reaction is being carried out in our laboratory.

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Supporting Information Available: Typical experimental procedure and analytical data for all the products. This material is available free of charge via the Internet at http://pubs. acs.org.

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(10) For the Pd(II)-catalyzed direct cyclization and dimerization of *terminal* allenyl ketones to afford a mixture of 2-monosubstituted furans and 2,4-disubstituted furans, see: (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1581−1583. (b) Hashmi, A. S. K.; Ruppert, T. L.; Kn'fel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295−7304. In most cases, the dimerization products are predominant, which limit the synthetic utility of this methodology.