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Efficient synthesis of 4-(2′-alkenyl)-2,5-dihydrofurans via $PdCl_2$-catalyzed coupling–cyclization reaction of 2,3-allenols with allylic halides

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Abstract

4-(2′-Alkenyl)-2,5-dihydrofurans can be efficiently synthesized via the $PdCl_2$-catalyzed coupling–cyclization of allylic halides with 2,3-allenols in DMA at rt in moderate to good yields. The regioselectivity is different from that of the Pd(0)-catalyzed coupling–cyclization of organic halides with 2,3-allenols.

2,5-Dihydrofurans, an important class of heterocyclic compounds, are useful intermediates for organic synthesis[1] and common structural units in many natural products.[2] These compounds are usually prepared via Ag(I)-catalyzed rearrangement–cyclization of 4-hydroxypropargyl esters,[3] dehydration of *cis*-2-alken-1,4-diols,[4] palladium-catalyzed reaction of cyclic alkynyl carbonates with electron-deficient alkenes,[5] Prins reaction of a terminal alkene and formaldehyde,[6] reaction of oxazirconacyclopentenes with propynoates,[7] cyclization of 2,3-allenols upon addition of electrophiles,[8] and Ag^+ or Hg^{2+}-catalyzed cycloisomerization reaction of 2,3-allenols.[8d–e,9] During the course of our study on the chemistry of functionalized allenes,[10–12] we have studied the Pd(0)-catalyzed coupling–cyclization reaction of 2,3-allenols with organic halides.[13] In all cases, the three-membered vinylic oxiranes were formed (Path A, Scheme 1) while the formation of the corresponding five-membered 2,5-dihydrofurans (Path B, Scheme 1) was not observed.[14] Even when R^2 was introduced to increase the steric hindrance at the 2-position of 2,3-allenols, the formation of 2,5-dihydrofurans was still not observed. Due to the substituent-loading capability (up to three) of 2,3-allenols, we are interested in the chemistry of the polysubstituted 2,5-dihydrofuran-formation reaction from 2,3-allenols and organic halides. In this letter, we wish to communicate our recent results on the $PdCl_2$-catalyzed coupling–cyclization reaction of 2,3-allenols with allylic halides. The advantage of this methodology is

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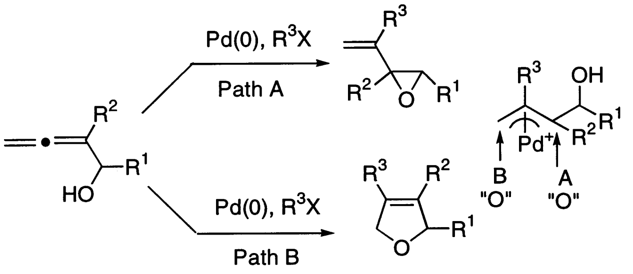
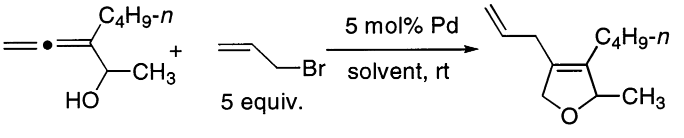


Scheme 1.

that an allylic group is introduced into the 4-position, which adds synthetic diversity and may be suitable for further elaboration.

After some trial and error, we observed that under the catalysis of 5 mol% of $PdCl_2$, the reaction of 3-(*n*-butyl)-3,4-pentadien-2-ol (**1a**) with 5 equiv. of allyl bromide afforded the expected five-membered product 2-methyl-3-(*n*-butyl)-4-allyl-2,5-dihydrofuran (**3a**) in 74% yield. The reaction in DMA with less than 5 equiv. of allyl bromide afforded **3a** in lower yields. When allyl chloride was used instead of allyl bromide, **3a** was obtained in 51% yield. $PdCl_2$ was found to be effective even at catalyst loading as low as 1 mol% and the corresponding reaction of **1a** with 5 equiv. of allyl bromide afforded **3a** in 65% yield. Several palladium catalysts including $PdCl_2$, $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$ and $[(\pi\text{-}C_3H_5)PdCl]_2$ were tested and all proved to be effective for this transformation. Due to its ready availability, we chose $PdCl_2$ as the catalyst.



1a **2a** **3a**

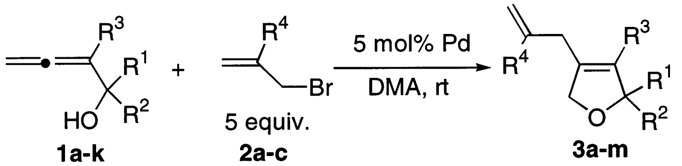
A series of 2,3-allenols **1a–i** were prepared[15] and their $PdCl_2$-catalyzed coupling–cyclization reaction with allyl bromide under the standard reaction conditions were studied;[16] some typical results are summarized in Table 1. With R^3 being alkyl, allyl, phenyl, or benzyl, the reaction of 2,3-allenols **1** with allyl bromide afforded the corresponding 4-(2′-alkenyl)-2,5-dihydrofurans **3** in moderate to good yields.

The reaction of 2,3-allenols with substituted allylic halides was also studied. Under the standard reaction conditions, the reaction of **1i** with a series of substituted allylic halides **2** was screened. We found that when 3-phenyl-2-propenyl bromide was used, the reaction was complicated. However, 2-substituted allylic bromides **2b–c** reacted smoothly with 2,3-allenol **1i** to afford the corresponding 2,5-dihydrofurans **3k–l** in good yields (entries 11–12, Table 1).

When 3-chloro-1-butene **2d**[17] was used as the allylating reagent, its reaction with **1a** afforded the S_N2'-type product **4** with high selectivity (Scheme 2).

In summary, we have developed a novel Pd-catalyzed coupling–cyclization reaction of 2,3-allenols with allylic halides, which provides an efficient route to polysubstituted 2,5-dihydrofurans. The reaction conditions are mild (rt), the catalyst $PdCl_2$ is readily available and air stable, the starting materials are readily available and the yields are moderate to good. Further studies on the scope, synthetic utility and the mechanism of this methodology are being carried out in our laboratory.

Table 1
PdCl$_2$-catalyzed coupling–cyclization reaction of 2,3-allenols with allylic bromides[a]

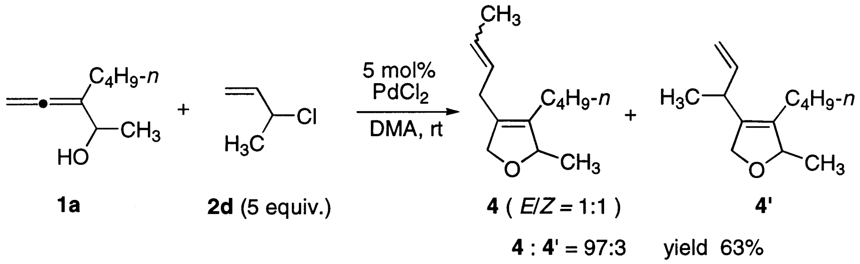


Entry	1			2	Time (h)	Yield of **3** (%)[c]
	R^1	R^2	R^3	R^4		
1	CH$_3$	H	n-C$_4$H$_9$(**1a**)	H (**2a**)	18.5	76 (**3a**)
2	n-C$_4$H$_9$	H	n-C$_4$H$_9$ (**1b**)	**2a**	10.5	81 (**3b**)
3	Ph	H	n-C$_4$H$_9$ (**1c**)	**2a**	21	81 (**3c**)
4	CH$_3$	H	CH$_3$ (**1d**)	**2a**	3.5	71 (**3d**)
5	n-C$_4$H$_9$	H	C$_3$H$_5$[b] (**1e**)	**2a**	2	64 (**3e**)
6	CH$_3$	H	PhCH$_2$ (**1f**)	**2a**	18.5	61 (**3f**)
7	n-C$_4$H$_9$	H	Ph (**1g**)	**2a**	14.5	68 (**3g**)
8	Ph	H	Ph(**1h**)	**2a**	14.5	60 (**3h**)
9	CH$_3$	CH$_3$	Ph (**1i**)	**2a**	9	86 (**3i**)
10	CH$_3$	CH$_3$	n-C$_4$H$_9$ (**1j**)	**2a**	23	57 (**3j**)
11	CH$_3$	CH$_3$	Ph (**1i**)	Ph (**2b**)	22.5	74 (**3k**)
12	CH$_3$	CH$_3$	Ph (**1i**)	Br (**2c**)	19	71 (**3l**)

[a] The reaction was carried out at rt using **1** (1 mmol), allylic bromide **2** (5 mmol) and PdCl$_2$ (0.05 mmol, 5 mol%) in DMA (6 mL).

[b] C$_3$H$_5$ = allyl.

[c] Isolated yield based on **1**.



Scheme 2.

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16. General procedure: A mixture of 2,3-allenol **1** (1 mmol), allylic halide **2** (5 mmol), $PdCl_2$ (5 mol%) was stirred in DMA (6 ml) at rt. When the reaction was complete, ether was added. The reaction mixture was washed with brine, dried over anhydrous Na_2SO_4. Flash column chromatography on silica with petroleum ether and ether as eluent afforded 2,5-dihydrofuran **3**.
17. 98% purity, purchased from Tokyo Kasei Kogyo Co., Ltd.