

# Pd<sup>0</sup>-catalyzed cyclization reaction of aryl or alk-1-enyl halides with 1,2-dienyl ketones: a general and efficient synthesis of polysubstituted furans

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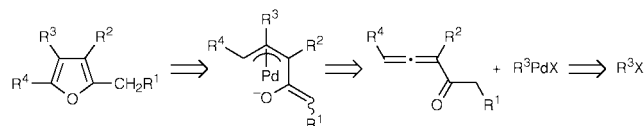
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Under catalysis by Pd<sup>0</sup> and Ag<sub>2</sub>CO<sub>3</sub>, the reaction of 1,2-allenyl ketones and organic halides in PhMe using Et<sub>3</sub>N as the base provides a new general access to polysubstituted furans with good to excellent yields.

Furans, one of the most prominent classes of heterocyclic compounds, can be found in many naturally occurring products,<sup>1</sup> commercially important pharmaceuticals, and flavor and fragrance compounds.<sup>2</sup> They are also considered as important synthetic intermediates for the preparation of numerous cyclic and acyclic compounds.<sup>3</sup> Usually, 3-, 2,3-, 2,4-, 3,4-, 2,3,4- and 2,3,5-substituted furans<sup>4</sup> can be synthesized *via* acyclic precursors or derivatization of simple furans.<sup>5</sup> Owing to its potential and diversity, much attention has been paid to the synthesis of furans from acyclic precursors. Some of the most important and interesting methodologies are as follows: (i) cyclization of alk-4-yn-1-ols;<sup>6</sup> (ii) cyclization of alk-3-yn-1-ols;<sup>7</sup> (iii) AlCl<sub>3</sub>-catalyzed cyclization of acyl chlorides with 1,2-allenyl silanes;<sup>8</sup> (iv) epoxidation and subsequent HgO-catalyzed cyclization of alk-1-enyl alk-1'-ynyl methanols;<sup>9</sup> and (v) Pd-catalyzed cyclization of (Z)-2-iodoalk-2-enyl ketones.<sup>10</sup>

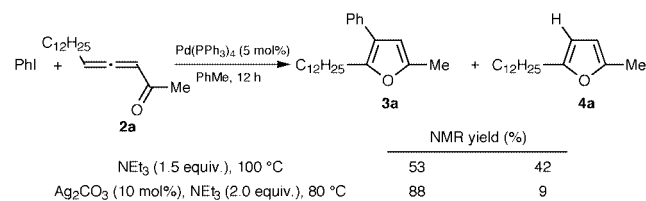
Recently, Marshall *et al.*<sup>11</sup> reported the Rh<sup>+</sup>- or Ag<sup>+</sup>-catalyzed direct one-component cyclization of 1,2-dienyl ketones to afford substituted furans with obvious limitations (mainly R<sup>3</sup> = H, Scheme 1). Since the introduction of



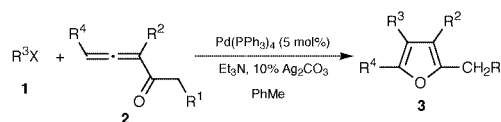
Scheme 1

substituents at the 3- and/or 4-position of the corresponding unsubstituted furans is difficult, efficient and general methodologies for furans with substituents at some or all of the four positions are still of current interest. During the course of our study of functionalized allenes,<sup>12,13</sup> we envisioned that a Pd<sup>0</sup>-catalyzed cyclization of an organic halide with a 1,2-dienyl ketone would provide an efficient and general route to polysubstituted furans with the unique assembly of substituents at the different positions, depending on the substitution of both reactants (Scheme 1).<sup>14</sup>

1,2-Dienyl ketones with different substitution patterns are easily available.<sup>12c,14b,15</sup> As a starting point, we studied the Pd<sup>0</sup>-



Scheme 2



R<sup>3</sup>X = PhI (**1a**)  
*p*-Nitrophenyl iodide (**1b**)  
*p*-Methoxycarbonylphenyl iodide (**1c**)  
 5-Bromopyrimidine (**1d**)  
 Methyl (Z)-3-iodopropenoate (**1e**)  
*p*-Methoxyphenyl iodide (**1f**)

Scheme 3

Table 1 Efficient synthesis of polysubstituted furans<sup>a</sup>

Entry	R <sup>3</sup> X <sup>b</sup>	Ketone 2				T/°C	t/h	Product (% yield) <sup>c</sup>
		R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>				
1	<b>1a</b> (2.0)	<b>2a</b>	H	H	C <sub>12</sub> H <sub>25</sub>	80	12	<b>3a</b> (75)
2	<b>1b</b> (2.0)	<b>2a</b>	H	H	C <sub>12</sub> H <sub>15</sub>	80	13	<b>3b</b> (90)
3	<b>1c</b>	<b>2a</b>	H	H	C <sub>12</sub> H <sub>15</sub>	80	14	<b>3c</b> (94)
4	<b>1a</b>	<b>2b</b>	H	H	Bu	80	12	<b>3d</b> (73)
5	<b>1b</b>	<b>2b</b>	H	H	Bu	80	9	<b>3e</b> (92)
6	<b>1c</b>	<b>2b</b>	H	H	Bu	80	9	<b>3f</b> (85)
7	<b>1d</b>	<b>2b</b>	H	H	Bu	80	11	<b>3g</b> (71)
8	<b>1e</b>	<b>2b</b>	H	H	Bu	80	11	<b>3h<sup>d</sup></b> (61)
9	<b>1c</b>	<b>2c</b>	H	Me	H	100	14	<b>3i</b> (68)
10	<b>1b</b>	<b>2c</b>	H	Me	H	100	11	<b>3j</b> (79)
11	<b>1d</b>	<b>2d</b>	H	Bu	H	100	17	<b>3k</b> (97)
12	<b>1b</b>	<b>2e</b>	H	H	Ph	80	10	<b>3l</b> (51)
13	<b>1c</b>	<b>2e</b>	H	H	Ph	80	10	<b>3m</b> (51)
14	<b>1b</b>	<b>2f</b>	Et	H	Ph	80	12	<b>3n</b> (77)
15	<b>1c</b>	<b>2f</b>	Et	H	Ph	80	12	<b>3o</b> (73)
16	<b>1f</b>	<b>2b</b>	H	H	Bu	80	11	<b>3p</b> (66)
17	<b>1f</b>	<b>2g</b>	H	H	C <sub>7</sub> H <sub>15</sub>	80	11	<b>3q</b> (63)

<sup>a</sup> Generally, the reaction was carried out using 1,2-allenyl ketone (1.5 equiv.), R<sup>3</sup>X (1.0 equiv.), and 5 mol% of Pd(PPh<sub>3</sub>)<sub>4</sub> in PhMe, unless otherwise stated.

<sup>b</sup> The numbers in the parenthesis are the equiv. of R<sup>3</sup>X used. <sup>c</sup> Isolated yield. <sup>d</sup> The configuration of the C=C bond in R<sup>3</sup> is *trans*.

catalyzed cyclization reaction of heptadeca-3,4-dien-2-one **2a** with PhI under various reaction conditions. After some screening, we found that the Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed cyclization reaction of PhI with **2a** afforded the expected product **3a** in 88% yield together with the formation of **4a** in only 9% yield by using 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> as the catalyst, toluene as the solvent, and Et<sub>3</sub>N (2.0 equiv.)–Ag<sub>2</sub>CO<sub>3</sub> (10 mol%) as the base. Similar to the cyclization reaction of 1,2-allenic carboxylic acids, we observed that a catalytic amount of Ag<sub>2</sub>CO<sub>3</sub> is crucial to this reaction (Scheme 2).

Using these standard conditions, we studied this new and efficient synthetic methodology for the synthesis of poly-substituted furans with differently substituted 1,2-dienyl ketones as well as different kinds of organic halides (Scheme 3). The results are summarized in Table 1.

The results in Table 1 show that (i) the yields for this reaction range from moderate to excellent, with the highest being 97% (entry 11, Table 1); (ii) both electron-rich and electron-deficient aryl halides afforded the corresponding furans; (iii) substituents at different positions of furans could be introduced, depending on the structure of allenyl ketones and organic halides; and (iv) the reaction of methyl (*Z*)-3-iodopropenoate<sup>16</sup> yielded the product **3h**, providing an opportunity for further elaboration of the substitutions at the 4-position (entry 8, Table 1).

In conclusion, we have developed an efficient method for the synthesis of substituted furans with different substitution patterns. The study of new methodologies for differently substituted 1,2-allenyl ketones and the scope of this cyclization reaction, as well as its application in the synthesis of target molecules with potential activities, are currently being carried out in our laboratory.

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