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Palladium catalyzed direct allylation of azlactones with simple allylic alcohols in the absence of any activators†

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The first example for the readily scalable direct allylic alkylation of azlactones with simple allylic alcohols has been developed, which is catalyzed by Pd(PPh3)4 alone in the absence of any activators under neutral conditions.

Palladium-catalyzed α-allylic alkylations of carbonyl compounds, namely Tsuji-Trost reaction, are powerful and widely used methodologies for C-C bond formation in the synthesis of pharmaceuticals, biologically active natural products, and materials. Generally, such reactions involve the allylic alkylation of nucleophiles with activated allylic alcohol derivatives as allylic species, for instance, carbonates, acetates, phosphates, amines and halides, which always generate stoichiometric waste (Scheme 1, eq.(1)). From the viewpoint of environmental issues and atom-/step-economy, the direct use of simple allylic alcohol itself as precursor of π-allyl fragment is much more attractive and practical for such kind of transformations, which gives only water as by-product. However, presumably suffering from the poor leaving capability of the hydroxyl group at allylic alcohol, extra activators are intrinsically required to activate in situ allylic alcohol for the success of allylation, including toxic inorganic acids, strong Lewis acids, and Brønsted acids (Scheme 1, eq.(2)). Despite great advances in Tsuji-Trost-type alkylations have defined the current state of the art in C-C bond-forming reactions, the direct use of simple allylic alcohol as allylating reagents in the absence of any activating reagents has rarely been achieved. Herein, we report the first example of Pd(PPh3)4 alone catalyzed highly efficient allylation of azlactones with simple unactivated allylic alcohols in the absence of any activators under neutral conditions (Scheme 1, eq.(3)). It is noteworthy that the approach provides a practical access to quaternary allylic amino acids via hydrolysis of the allylated azlactones, which is of great potential in the synthesis of biologically active molecules.

Inspired by the Pd/Brønsted acid co-catalyzed allylation, in which the hydrogen bonding between Brønsted acid and allylic alcohol played a critical role for the generation of π-allyl-Pd intermediate that propel the following allylic process (Scheme 2, eq. (1)), we reasoned that the extra addition of Brønsted acid might be not necessary if allylic alcohol can be activated by substrateself via hydrogen bonding (Scheme 2, eq. (2)). Upon this hypothesis, azlactone A is selected as the starting material owing to its tautomerization to 5-hydroxyl-oxazole B. The latter might react with allylic alcohol via hydrogen bonding (C) to expel the hydroxyl group, followed by insertion of Pd(0) catalyst for the generation of the key π-allyl-Pd intermediate D; then D gives the desired allylated adduct E (Scheme 2, eq. (3)).

Scheme 1 Profile of Tsuji-Trost-type allylation reaction.

Scheme 2 Activation modes of allylic alcohol and the working hypothesis.
Gratifyingly, the treatment of azlactone 1a with two equiv of allylic alcohol 2a in the presence of 5.0 mol % Pd(PPh₃)₄ and 4Å molecular sieves (4Å MS) in toluene at 60°C for 12 h provided the allylated product 3a in almost quantitative yield smoothly (Table 1, entry 1). Remarkably, even reducing the Pd(PPh₃)₄ loading to 1.5 mol % didn’t affect the yield (entry 2). Lowering the reaction temperature from 60°C to 40°C resulted in 75% yield (entry 3). A belief examination of the solvent effect revealed toluene as the solvent of choice. Changing the solvent to ethyl acetate (EA) and methyl-tert-butylether (MTBE) lowered the yield of 3a to 40% and 20%, respectively (entries 4 and 5).

**Table 1** Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(PPh₃)₄ (mol %)</th>
<th>T°C</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0</td>
<td>60</td>
<td>Toluene</td>
<td>&gt;99%(98%)</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>60</td>
<td>Toluene</td>
<td>&gt;99%(97%)</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>40</td>
<td>Toluene</td>
<td>75%</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>40</td>
<td>EA</td>
<td>40%</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>40</td>
<td>MTBE</td>
<td>20%</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 1a (0.2 mmol), 2a (0.4 mmol), 4Å MS (50 mg), solvent (1.0 mL). † Determined by ‘H NMR analysis of the crude reaction mixture. ‡ Isolated yield in the parenthesis.

With the optimized reaction conditions in hand, our attention was turned to investigation of the substrate scopes with respect to azlactones and allylic alcohols. First, a series of azlactones were employed as the nucleophiles. Gratifyingly, the protocol is quite general and tolerates azlactones bearing a range of substitutes, including electron-withdrawing and electron-donating groups (Table 2). Besides 1a, treatment of azlactones 1b-d substituted with a chlorine atom at the para-position with 2a in the presence of 1.5 mol % Pd(PPh₃)₄ and 4Å MS at 60°C in toluene for 12 hours, the corresponding allylated adducts 3b-d efficiently formed in 91%, 90%, and 87% yield, respectively. Azlactone 1e, with a chlorine atom at the ortho-position, furnished 3e in 86% yield as well. Bearing the aryl group with electron-donating substituent, such as methoxyl and methyl group, 1f-j gave the desired products 3f-j in 70->99% yield; even the reaction enlarged to two-gram scale, 3g was readily isolated in 97% yield.

Substrates having different electronic properties of benzyl groups at the 4-position of the oxazolone ring could also undergo the direct allylation reaction smoothly, affording 3k-n in 82->99% yield. Interestingly, the nucleophile 1o derived from tryptophan with an unprotected N-H group was surprisingly well tolerated, resulting in the allylated product 3o in 90% yield. Employing bulky substituted azlactones having 4-cyclopentyl (1p) and 4-cyclohexyl group (1q) under the mild reaction condition, the direct allylation processes proceeded in both 77% yield. Strikingly, the replacements of methyl (1g) with much more hindered tert-butyl (1r) and naphthalen-2-ylmethyl group (1s) are also applicable to the allylation reaction, and the reactions afforded 3r,s in 94% and 85% yield respectively, although a slightly increased Pd(PPh₃)₄-loading to 3.0 mol % were required for complete substrate conversions.

**Table 2** Direct allylation of azlactones with allylic alcohol 2a<sup>ad</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic alcohol</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>3t</td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td>3t</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>3u</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>3v</td>
<td>97%</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>3w</td>
<td>89%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1g (0.2 mmol), 2b-c (0.24 mmol), Pd(PPh₃)₄ (1.5 mol %), 4Å MS (50 mg), toluene (1.0 mL), 60°C, 12 h; All yields are isolated. <sup>b</sup> 3.0 mol % of Pd(PPh₃)₄ used.

Importantly, we were pleased to find that the practical direct allylic alkylation reaction can be easily extended to a range of substituted allylic alcohols (Table 3). Consequently, the treatment of 1g with five substituted allylic alcohols 2b-f facilely led to...
allylated products 3t-w in 78-97% yields. It is noteworthy that the reactions of 1g with both 2h and 2c exclusively afforded 3t (entries 1 and 2) in similar yields, which indicate that both reactions proceeded via the same π-allyl-Pd intermediate.5

Remarkably, allylic alcohol 2f bearing highly steric hindrance is also suitable for the process, the reaction afforded 3w in 89% yield smoothly.

In conclusion, we have developed an efficient direct allylic alkylation of azlactones with simple allylic alcohols using Pd(PPh3)4 alone as catalyst under neutral conditions by substrateself-assisted activation strategy. The approach can be easily extended to gram scale in almost quantitative yield, which provides a practical synthetic approach to quaternary allylic amino acids. Further applications of the practical method, as well as the asymmetric variant of this reaction are underway in our laboratory and will be reported in due course.

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Notes and references


7 Very recently, Hartwig and Chen reported an example that is iridium-catalyzed diastereo- and enantioselective alkylations of substituted SH-oxazol-4-ones with acetates and carbones under strong basic conditions, see: W. Chen, J. F. Hartwig, J. Am. Chem. Soc. 2014, 136, 377.
