Palladium-catalyzed Synthesis of Terminal Acetals via Highly Selective Anti-Markovnikov Nucleophilic Attack of Pinacol on Vinylarenes, Allyl Ethers, and 1,5-Dienes

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A palladium-catalyzed reaction of vinylarenes, allyl ethers, and 1,5-dienes with pinacol proceeded via a selective anti-Markovnikov nucleophilic attack to afford corresponding terminal acetals as major products. The bulkiness of pinacol was found to be critical in controlling the regioselectivity.

The achievement of anti-Markovnikov regioselectivity in the Wacker oxidation is challenging, but can enable an attractive, direct transformation from terminal alkenes to aldehydes. Although the reaction generally proceeds in a Markovnikov manner to afford methyl ketones, alkenes bearing a heteroatom directing group, as well as vinylarenes, often afford aldehydes preferentially. Even with these substrates, however, the regioselectivity appears to still be susceptible to various reaction conditions. The situation is similar in the palladium-catalyzed acetalization of terminal alkenes with alcohols. Internal acetals are usually major products, whereas electron-deficient α,β-unsaturated carbonyl compounds and alkenes with a directing group afford terminal acetals. Alkenes with two hydroxyl groups (3-methylidene-1,5-diols) also give terminal acetals via intramolecular acetalization. In the case of vinylarenes, the regioselectivity is known to be mainly affected by the ligands on palladium. A PdCl₂/CuCl₂/dimethoxyethane (DME) system gives terminal acetals, whereas a PdCl₂(sparteine)/CuCl₂/O₂/Methanol system affords internal acetals.

Another potential factor is the steric demand of nucleophiles. In the reported Wacker oxidations of terminal alkenes, the use of R-BuOH as a solvent produced aldehydes selectively, although the yields were generally low. In these reactions, R-BuOH would operate as a nucleophile to afford linear alkenyl R-butyll ethers and/or terminal acetals via alkoxypropagation, and subsequent hydrolysis gives aldehydes; however, the ethers and acetals appear to be elusive because of the facile hydrolysis by a trace of water. In this context, during the course of our investigation on the reaction of terminal alkenes with diols, we found that the steric demand of the diols critically influenced the regioselectivity to give terminal acetals. Herein, we report the palladium-catalyzed reliable synthesis of terminal acetals from vinylarenes, allyl aryl ethers, and 1,5-dienes, controlling the selectivity in an anti-Markovnikov manner by using a bulky tertiary diol, pinacol (eq 1).

With styrene as a terminal alkene and several 1,2-diols having different steric bulkiness as nucleophiles, the regioselectivity of the nucleophilic attack was first examined in the presence of PdCl₂(MeCN)₃ (10 mol%) and p-benzoquinone (2.0 eq) in N,N-dimethylformamide (DMF, Table 1). When ethylene glycol, 2-methyl-1,2-propanediol, and 2,3-butanediol were employed, the formation ratios of the terminal acetals 2a–c and the internal acetals 3a–c were close to 1:1 (entries 1–3), along with the formation of a certain amount of acetophenone derived from styrene and a trace of contaminated water. It is noteworthy that the use of pinacol critically influenced the regioselectivity, giving 2d in preference to 3d in the ratio of >95:5 (entry 4). These results indicate that the steric bulkiness of the diol controls the regioselectivity to the terminal carbon in the nucleophilic attack of the diol on the coordinated styrene.

The reaction conditions using pinacol were applied to various vinylarenes (Table 2). Styrenes with an electron-withdrawing substituent such as chloro, nitro, or trifluoromethyl groups gave

![Reaction conditions: 1a (0.6 mmol), diol (6.0 mmol), PdCl₂/MeCN]₂ (0.06 mmol), p-benzoquinone (1.2 mmol), and DMF (0.6 mL). Determined by H NMR. GC yield. Isolated yield is shown in parentheses. Table 1. Steric effect of 1,2-dials on the regioselectivity in palladium-catalyzed acetalization of styrene.

| Entry | Diol | Product | Total Yield of 2 and 3 (%) | Ratio of 2:3
<table>
<thead>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>HO</td>
<td>2a, 3a</td>
<td>48</td>
<td>52:48</td>
</tr>
<tr>
<td>2</td>
<td>HO</td>
<td>2b, 3b</td>
<td>66</td>
<td>55:45</td>
</tr>
<tr>
<td>3</td>
<td>HO</td>
<td>2c, 3c</td>
<td>58</td>
<td>56:44</td>
</tr>
<tr>
<td>4</td>
<td>HO</td>
<td>2d, 3d</td>
<td>72 (60)</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

Reaction conditions: 1a (0.6 mmol), diol (6.0 mmol), PdCl₂/MeCN]₂ (0.06 mmol), p-benzoquinone (1.2 mmol), and DMF (0.6 mL). Determined by H NMR. GC yield. Isolated yield is shown in parentheses.
Table 2. Palladium-catalyzed synthesis of terminal acetals from vinylarenes and pinacol

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>total yield of 2 and 3 (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2e</td>
<td>73 (69)</td>
</tr>
<tr>
<td>2</td>
<td>2f</td>
<td>79 (75)</td>
</tr>
<tr>
<td>3</td>
<td>2g</td>
<td>76 (72)</td>
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<tr>
<td>4</td>
<td>2h</td>
<td>83 (58)</td>
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<tr>
<td>5</td>
<td>2i</td>
<td>64 (59)</td>
</tr>
<tr>
<td>6</td>
<td>2j</td>
<td>68 (58)</td>
</tr>
<tr>
<td>7</td>
<td>2k</td>
<td>39 (33)</td>
</tr>
<tr>
<td>8</td>
<td>2l</td>
<td>71 (49)</td>
</tr>
<tr>
<td>9</td>
<td>2m</td>
<td>61 (51)</td>
</tr>
<tr>
<td>10</td>
<td>2n</td>
<td>50 (46)</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 (0.6 mmol), pinacol (6.0 mmol), PdCl₂(MeCN)₂ (0.06 mmol), p-benzoquinone (1.2 mmol), and DMF (0.6 mL). GC yields. Isolated yields are shown in parentheses. A small amount (5%) of 2-naphthylcarboxaldehyde acetal was obtained along with 2n.

The corresponding terminal acetals 2e-h in good yield (entries 1-4). On the other hand, styrenes with an electron-donating substituent such as methyl or methoxy groups were also applicable but the yields of 2i-m were relatively low (entries 5-9). The existence of the substituent at the ortho position did not disturb the reaction in terms of steric hindrance (entries 2, 6 and 12). 2-Vinylindole was suitable as a substrate as well, but a small amount (5%) of 2-naphthylecarboxaldehyde acetal was also obtained (entry 10). The reaction of 2- and 4-vinylindoles did not proceed, probably due to the coordination of the pyridyl group to palladium to deactivate the catalyst. As an α-substituted vinylarene, α-methylstyrene was tested; however, no terminal acetal was observed and a large portion of the substrate remained unreacted.

Allyl aryl ethers were then examined as substrates (Table 3). These reactions proceeded in shorter reaction time than those with vinylarenes. When allyl phenyl ether (4a) was employed, the desired terminal acetal 5a was obtained along with internal acetal 6a in 75% total yield in the ratio of 88:12 (entry 1). For comparison, the reaction of 4a with ethylene glycol was also carried out under the same reaction conditions, and the formation ratio of terminal to internal acetals was 49:51 (88% total yield), once again clearly demonstrating the steric effect of pinacol. In the reaction shown in entry 1, however, not only the acetals 5a and 6a but also 3-methylbenzofuran (7) was formed in 14% yield, which was derived from only 4a. As a control experiment, we tried the same reaction in the absence of pinacol, and 7 was obtained in 51% yield. Such Fujiwara-Moritani oxidative Heck cyclization of allyl aryl ethers with electron-donating groups to afford 3-methylbenzofurans was previously reported by Stoltz et al. In order to suppress the side reaction, allyl aryl ethers having an electron-withdrawing substituent (entry 2) or methyl groups at ortho positions (entry 3) were employed. In these cases, the formation of 3-methylbenzofurans was suppressed and terminal acetals 5b and 5c were obtained in good to high yield, along with small amounts of internal acetals 6b and 6c.
respectively. Allyl p-hexyl ether was also examined as an alkyl analog under similar reaction conditions as listed in Table 3. While most of the substrate was consumed, the yield of the corresponding terminal acetal appeared to be low, ca. 10–20%.

The present procedure was also applied to 1,5-hexadiene (8) because 1,5-diene derivatives are known to afford aldehydes under Wacker oxidation conditions.21,22 Although the yield was relatively low, corresponding terminal acetal 9 along with cyclized internal acetal 10 were obtained in the ratio of 87:13 (eq 2). Prolonged reaction time decreased the yield of 9. The reaction of 8 with ethylene glycol resulted in the ratio of 68:32 for terminal/cyclized internal acetals. In the reaction of 4-vinylexohexene (11), terminal acetal 12 was afforded in 44% yield exclusively (eq 3). Other a,ω-dienes such as diethyl diallylmalonate and 1,7-octadiene resulted in no formation of terminal acetals.

A proposed reaction mechanism for the present acetalization using styrene as a terminal alkene is shown in Scheme 1. Styrene first coordinates to the Pd(II) species in an η5 manner (13), and then, the first nucleophilic attack of pinacol on the coordinated styrene occurs in anti-Markovnikov regioselectivity to form α-benzyl intermediate 14. At this stage, the nucleophilic attack on the internal carbon would be unfavorable because the steric repulsion between the phenyl group and the pinacol is greater. This repulsion is especially effective when pinacol is used compared with other less bulky diols, as listed in Table 1. The formed 14 is in equilibrium with α-benzyl intermediate 15, from which β-hydrogen elimination occurs to give alkanyl ether-coordinated palladium hydride species 16. Either palladium-assisted or acid-promoted cyclization from 16 would proceed to afford the terminal acetal 2d along with the formation of Pd(0), which is oxidized by p-benzoquinone to reproduce the catalytically active Pd(II) species. The formation of the α-benzyl intermediate is considered a significant factor in controlling the regioselectivity in an anti-Markovnikov manner in the previously reported palladium-catalyzed Wacker oxidation,4 acetalization14 and oxidative amination3 of vinylarenes. On the other hand, in the reactions of allyl aryl ethers and 1,5-diienes, the appropriately located oxygen atom or alkene moiety would operate as a directing group to assist the nucleophilic attack of pinacol on the terminal carbon.1,14

In summary, a reliable, palladium-catalyzed method for synthesizing terminal acetals from vinylarenes, allyl aryl ethers, and 1,5-diienes has been established. In the present reaction, the nature of the substrates and the steric bulkiness of the pinacol synergistically controlled the regioselectivity in an anti-Markovnikov manner. Further investigations for oxidative heterofunctionalization reactions of terminal alkenes based on the present strategy using bulky nucleophiles are in progress.

**Notes and references**

18. Recently, synthesis of primary alcohols by formal hydration of terminal alkenes taking advantage of anti-Markovnikov Wacker oxidation was reported. t-BuOHi is a key nucleophile in this reaction as well. Alkynyl t-butyl ethers were observed by 'H NMR spectroscopy and GC-MS, albeit in low yield, as a mixture with an aldehyde. See: G. Dong, P. Teo, Z. K. Wickens and R. H. Grubbs, Science, 2011, 333, 1609-1612.
24. For an example of the assistance of another alkene moiety as a directing group, see: M. G. Speziali, V. C. V. Costa, P. C. A. Robles-Dutenhefner and E. V. Gusevskaya, Organometallics, 2009, 28, 3186-3192.