

## Platinum(II)-catalyzed Annulation of 5-Methyl-5-hexen-1-ols with Aldehydes

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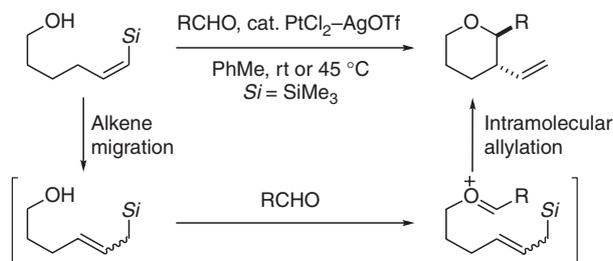
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In the presence of catalytic amounts of PtCl<sub>2</sub> and AgOTf, 5-methyl-5-hexen-1-ol reacted with aldehydes to give 2,3-disubstituted tetrahydropyrans in moderate to high yields with trans-stereoselectivity. Use of 5-methyl-5-hexen-1-ols bearing a methyl group at the C1-, C2-, or C3-position led to highly stereoselective synthesis of trisubstituted tetrahydropyrans.

Stereoselective construction of substituted cyclic ethers is an important subject in organic synthesis since these frameworks frequently appear in biologically active organic molecules.<sup>1</sup> The Brønsted or Lewis acid-promoted reaction of alkenols with aldehydes and acetals provides a convenient route to cyclic ethers.<sup>2-4</sup> The key step of this annulation is intramolecular addition of an alkene to an oxocarbenium ion intermediate. In general, the cyclization step is accompanied with deprotonation leading to ene products or with carbon-heteroatom bond formation by nucleophilic addition.

We have previously reported that the Pt<sup>II</sup>-catalyzed reaction of (*Z*)-6-trimethylsilyl-5-hexen-1-ol with aldehydes gives trans-2,3-disubstituted tetrahydropyrans (THPs) with high stereoselectivity (Scheme 1).<sup>5</sup> The reaction mechanism involves alkene migration of the vinylsilane and subsequent annulation of the resultant allylsilane with an aldehyde via an oxocarbenium ion intermediate. In view of the reactivity of oxocarbenium ions toward the ene-type cyclization, we anticipated that a similar annulation would occur with simple alkenes. Our initial trial with 5-hexen-1-ol resulted in failure; however, use of 5-methyl-5-hexen-1-ol (**1**) was found to enable a successful annulation under catalysis by PtCl<sub>2</sub>-AgOTf. We herein report the Pt<sup>II</sup>-catalyzed annulation of alkenol **1** and the related alkenols with aldehydes.

In the presence of PtCl<sub>2</sub> (0.5 mol %) and AgOTf (1 mol %), **1** reacted with benzaldehyde (**2a**) to give trans-2,3-disubstituted THP **3a** in 77% yield (Entry 1 in Table 1).<sup>6,7</sup> The cis isomer and 3-methylene-THP **4a** were also obtained as by-products. The formation of **4a** is attributable to alkene migration of **3a** followed by 1,3-allylic transposition.<sup>5</sup> The annulation hardly proceeded without AgOTf or PtCl<sub>2</sub>. Other aldehydes also underwent the Pt<sup>II</sup>-catalyzed annulation. Aromatic aldehydes **2b-2d**, bearing an electron-withdrawing group, achieved good to high



Scheme 1. Previous work on Pt<sup>II</sup>-catalyzed annulation.

Table 1. Pt<sup>II</sup>-catalyzed annulation of **1** with aldehydes

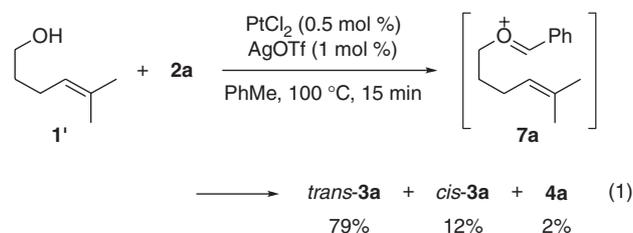
Entry	Aldehyde		Isolated yield/%		
	R	<b>2</b>	<i>trans</i> - <b>3</b>	<i>cis</i> - <b>3</b>	<b>4</b>
1	Ph	<b>2a</b>	77	<9 <sup>b</sup>	7
2	4-F-C <sub>6</sub> H <sub>4</sub>	<b>2b</b>	75	<17 <sup>b</sup>	7
3	4-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>	<b>2c</b>	77	7	0
4	4-NC-C <sub>6</sub> H <sub>4</sub>	<b>2d</b>	85	8	0
5	4-MeO-C <sub>6</sub> H <sub>4</sub>	<b>2e</b>	<37 <sup>b</sup>	0	0
6	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	<b>2f</b>	65	0	9
7	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	<b>2g</b>	59	0	8

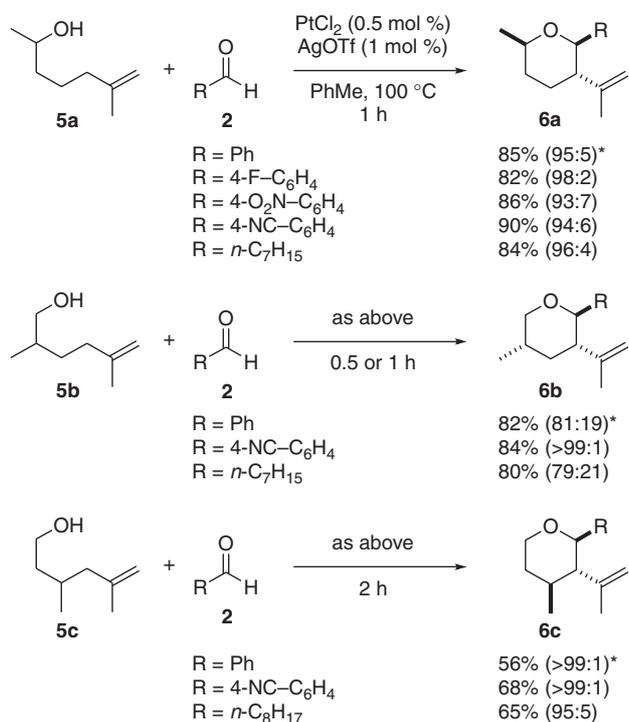
<sup>a</sup>All reactions were carried out with **1** (2.00 mmol), **2** (1.00 mmol), PtCl<sub>2</sub> (0.005 mmol), and AgOTf (0.010 mmol) in toluene (3 mL). <sup>b</sup>The product was contaminated with unidentified impurities.

yields of **3** (Entries 2–4). 4-Methoxybenzaldehyde (**2e**) caused a complex reaction (Entry 5). The annulation with aliphatic aldehydes **2f-2g** showed high trans-selectivity (Entries 6 and 7).

The Pt<sup>II</sup>-catalyzed annulation is applicable to the stereoselective synthesis of 2,3,*n*-trisubstituted THPs in which all substituents occupy the equatorial positions (Scheme 2).<sup>6</sup> The reactions of alkenols **5a** and **5b** afforded *r*-2,*t*-3,*c*-6-, and *r*-2,*t*-3,*t*-5-trisubstituted THPs (**6a** and **6b**), respectively, in high yield with good to high diastereoselectivity. In contrast, the annulation of **5c** leading to *r*-2,*t*-3,*c*-4-trisubstituted THPs **6c** was relatively slow and less efficient although high levels of diastereoselectivity were achieved.

To gain a mechanistic insight, we carried out the reaction of alkenol **1'** with **2a**. As a result, it was completed within 15 min to give **3a** and **4a** in high total yield (eq 1). Thus, both reactions using **1** and **1'** gave similar results. The annulation of **1'** proceeds most probably by the ene-type reaction of oxocarbenium ion **7a**,<sup>3c</sup> therefore, the annulation of **1** would also involve an oxocarbenium ion intermediate such as **7a**.

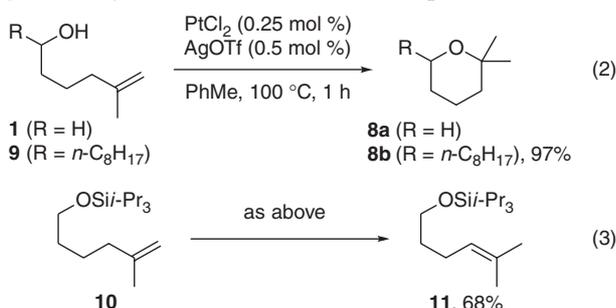




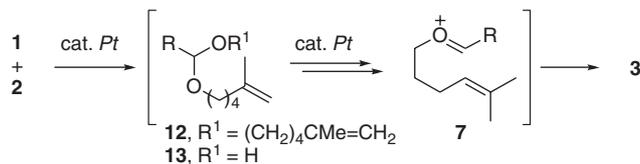
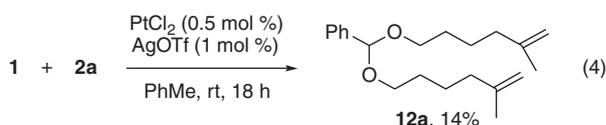
\*Isolated yield (major isomer : minor isomers).

### Scheme 2. Pt<sup>II</sup>-catalyzed annulation of alkenols **5a**–**5c**.

To ascertain the isomerization of **1** to **1'**, the reaction of **1** without aldehydes was performed under the same conditions. However, **1'** was not obtained at all, and the formation of THP **8a**, a volatile compound, was observed. A similar reaction of alkenol **9** gave THP **8b** in quantitative yield (eq 2). On the other hand, TIPS-protected alkenol **10** underwent alkene migration to give trisubstituted alkene **11** (eq 3).<sup>8</sup>



The Pt<sup>II</sup>-catalyzed reaction of **1** with **2a** at room temperature afforded acetal **12a** without **3a** (eq 4). The isolated acetal was converted into **3a** (ca. 60% yield) under catalysis by PtCl<sub>2</sub>–AgOTf at 60 °C. These results indicate that addition of the hydroxy group to the carbonyl group precedes alkene migration in the present annulation.



### Scheme 3. A plausible mechanism for annulation of **1** with **2**.

A plausible mechanism for the annulation of **1** is as follows (Scheme 3). The initial step is the reaction of an aldehyde with the hydroxy group. The resulting intermediate, an acetal **12** or a hemiacetal **13**, undergoes alkene migration and elimination of the alkoxy or hydroxy group to give an oxocarbenium ion **7**. The ene-type reaction of **7** affords the annulation product **3**. The Pt<sup>II</sup>-catalysis would serve for all steps except the last cyclization step.

In conclusion, we have developed a novel type of annulation of alkenols with aldehydes, which proceeds by a Pt<sup>II</sup>-catalyzed tandem process including alkene migration and the ene-type reaction of an oxocarbenium ion intermediate. The present annulation is quite valuable for the stereoselective synthesis of substituted THPs.

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