General, Simple and Chemoselective Catalysts for the Isomerization of Allylic Alcohols - The Importance of the Halide Ligand

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Abstract: Remarkably simple Ir(III) catalysts for the isomerization of primary and sec-allylic alcohols under very mild reaction conditions are reported. X-ray adsorption spectroscopy (XAS) and mass spectrometry (MS) studies indicate that a halide ligand is essential for catalytic activity.

Isomerization reactions involving functional group interconversions are highly important in organic synthesis. This is the case of the transition metal-catalyzed isomerization of allylic alcohols.[1, 2] Allylic alcohols are therefore catalysts for preparing carbonyl compounds, and even functionalized ones.[3] From a total synthesis perspective, one can take advantage of the distinct reactivity of these two functional groups in the design of synthetic routes, or can use available naturally occurring allylic alcohols as carbonyl precursors.

Despite existing several protocols,[4–11] a general and simple catalytic system able to isomerize selectively and efficiently both primary and sec-allylic alcohols under mild conditions has remained a challenge. The scope is commonly limited to molecules with few substituents, in particular for sec-allylic alcohols. An important example has recently been reported,[12] where a Pd hydride mediates the isomerization of primary and sec-allylic alcohols and remotely functionalized olefins. Current protocols usually need high catalyst loadings, chlorinated or aromatic solvents, activators or high temperatures. Also, the sophisticated ligands in the majority of these reports require additional synthetic effort. With a few exceptions,[14,15] each catalyst isomerizes exclusively either primary or sec-allylic alcohols efficiently. Each of these families trend to follow distinct isomerization mechanisms: whereas sec-allylic alcohols form enone intermediates,[15a,9] primary ones isomerize through migratory insertion/[i]-hydride elimination sequences.[10–12] For the latter, transition-metal hydrides have given excellent results under mild conditions, enabling enantioselective isomerizations.[14a,10,14]

We hereby report the isomerization of primary and sec-allylic alcohols using remarkably simple and commercially available P,N-ligandless Ir(III) complexes. Allylic alcohols with one, two, or three substituents on the double bond, in aqueous solvents, and even at room temperature and under an atmosphere of air were isomerized. Insights into the structure of the active catalyst were obtained by MS and XAS. Mechanistic investigations are also presented.

We have previously reported the synthesis of α-halocarbonyls from allylic alcohols catalyzed by [Cp*Ir(III)] complexes.[5] However, the simple isomerization reaction did not take place, or represented a minor pathway. To investigate whether the isomerization could occur under similar conditions, we reacted 1a with I–III (Table 1). Under the conditions previously used with [Cp*Ir(H2O)3]SO4 (I) and [(Cp*Ir2(OH)3)OH (II),[26] without halogenating agent, 1a was recovered (entries 1–4). In contrast, using [Cp*IrCl2] (III) in THF or acetone/H2O mixtures, afforded 2a in 85–99% in 30 min (entries 5–6).

Table 1. Isomerization of 1a by [Cp*Ir(III)].

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Solvent (v/v)</th>
<th>t (h)</th>
<th>Conv./Yield[^d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>THF:H2O (1:2)</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>Acetone:H2O (2:1)</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>II</td>
<td>THF:H2O (1:2)</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>II</td>
<td>Acetone:H2O (2:1)</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>III</td>
<td>THF:H2O (1:2)</td>
<td>0.5</td>
<td>85/85</td>
</tr>
<tr>
<td>6</td>
<td>III</td>
<td>Acetone:H2O (2:1)</td>
<td>0.5</td>
<td>&gt;99/97</td>
</tr>
</tbody>
</table>

[^d]: Supported by information for this article is given via a link at the end of the document.
The scope was then evaluated (Table 2). Excellent yields (95-99%) were obtained at RT with terminal aliphatic sec-allylic alcohols 1a-g, and functional groups such as ketones, ethers, and esters were tolerated (2d-f). The isomerization of olefin-functionalized 1f indicated selectivity for allylic alcohols, which was further confirmed with homoallylic 1h. Aromatic 1i-k afforded the products in moderate to good yields. Alcohols with 1,2-disubstituted double bonds (1l-p) were also isomerized in excellent yields. sec- Allylic alcohols with 1,1-disubstituted double bonds, of which reported examples are rare,[4a,5] afforded 2q-s in excellent yields at 60 °C for 2q-r, and at 100 °C for 2s. Other challenging substrates with a 1,1,2-trisubstituted double bond (1i) and cyclic 1u were isomerized in excellent and moderate yields, respectively. sec-Allylic alcohols with 1,2,2-trisubstituted or tetrasubstituted double bonds did not isomerize. Interestingly, even primary allylic alcohols (1v-1z) reacted smoothly at room temperature and the corresponding aldehydes 2v-2z were obtained in excellent yields.

**Table 2. Scope.**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>Reaction Conditions</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>O</td>
<td>H</td>
<td>H</td>
<td><a href="IV">Cp*IrCl2</a>, 1 mol%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>O</td>
<td>O</td>
<td>H</td>
<td>Ph</td>
<td>Acetone/H2O (2:1) RT</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>BrO</td>
<td>O</td>
<td>H</td>
<td>H</td>
<td>Acetone/H2O (2:1) 60 °C</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Ph</td>
<td>O</td>
<td>H</td>
<td>H</td>
<td>Acetone/H2O (2:1) RT</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>BnO</td>
<td>O</td>
<td>H</td>
<td>H</td>
<td>Acetone/H2O (2:1) 60 °C</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

[a] See SI. Yields by 1H NMR, in parentheses isolated. [b] [Cp*IrCl2](IV). [c] III (0.5 mol%) >95%, 0.5 h. [d] PrOH, III (2.5 mol%), Ar at 100 °C (uv). [e] From Z-1aa, 60 °C. [f] Degassed, 60 °C.
good yields. The Z conformer of allylic alcohol 1aa also reacted in good yield by increasing the temperature to 60 °C. Even 1ab with a 1,1,2-trisubstituted double bond was isomerized in moderate yield. These results are remarkable, since in hydrogen transfer to aldehydes Cp*Ir can show extremely high rates. However, under our reaction conditions, reduction of the product aldehydes yielding saturated alcohols was not detected.[15]

The compatibility with functional groups in complex molecules was demonstrated with morphine (5) and codeine (6).[16] Due to solubility, H₂O was replaced by PrOH (SI), which resulted in excellent yields of hydromorphone (7) and hydrocodone (8) (Scheme 1). Interestingly, in pure PrOH, analgesics dihydromorphine (9) and dihydrcodeine (10) were obtained via consecutive isomerization/transfer hydrogenation. A yield of 84% was obtained in the large-scale isomerization of 6 (72 g) by III (0.05 mol%).

Mechanistic investigations were undertaken to understand the lack of reactivity of halogen-free complexes. Addition of a substoichiometric amount of the brominating agent 4 (5 mol%) to the reactions shown in Table 1, entries 2 and 4, did result in formation of isomerization product 2a in 40 and 30% yield after 30 min, with I and II respectively (Scheme 2).[17]

When complex II was treated with an excess of 4 (SI), an orange solid precipitated (labeled as II/4). By MS the cation [Cp*IrBr]⁺ was identified (Figure S5), and neither I or II were detected. Ir L₃-edge XAS was used to obtain further information about the local environment around Ir.[17] The Ir L₃-edge X-ray absorption near edge structure spectroscopy (XANES) spectra of II/4 and of [Cp*IrBr]₂ (IV) are similar. The position of the white line and the corresponding 2p-5d electronic transition is detected at ~11214 eV (Figure 1, left). This energy is assigned to Ir(III) with similar coordination environments.[17] The Fourier-transformed X-ray absorption fine structure (EXAFS) spectra of II/4 is dominated by peaks at R = 1.76 and 2.22 Å (without correcting for phase-shifts and thus corresponding to 2.13 and 2.55 Å), associated with Ir−Cl or O and Ir−Br interactions respectively; the peak linked to Ir−Br bonds was not found for II (Figure 1, right).

The EXAFS data for II/4 were fitted against a structural model based on crystallographic data of [Cp*IrBr]₂ (IV), and matches with the presence of Br-bridging in this octahedral dimer (Table S5). It can be concluded that I and II react with 4 to form in situ complex of the general formula [Cp*IrBrX]₃, and that these are the catalytically active species, agreeing with the lack of activity of I−II in the isomerizations. This is supported by the excellent results also obtained with catalyst [Cp*IrBr]₂ (IV, Table 2).

![Figure 1](image-url)
We carried out mechanistic investigations to elucidate whether the reaction follows a migratory insertion/β-hydride elimination sequence (A, Scheme 3) or takes place via enone intermediates (B). An alternative Mechanism C via π-allyl intermediates was also considered.\(^{18}\)

The investigations were performed with sec-alcohols 1l and 1p, and with primary 1x and 1z. Isomerization of 1l-d\(_1\) afforded 2l-d\(_1\), with deuterium exclusively at C\(_\beta\) (Scheme 4). In contrast, deuterium was found in both C\(_\alpha\) and C\(_\beta\) in 2p-d\(_1\). For primary 1z-d\(_2\), deuterium was not detected at C\(_\alpha\) and one deuterium was exclusively transferred to C\(_\beta\) (SI). In all cases, the deuterium content in the products corresponded well with that in the alcohols.

In a double cross-over experiment, scrambling of deuterium between substrates did not occur for any type of alcohol (Scheme 5 and SI).

A non-competitive KIE of 1.2 was determined for 1l-d\(_1\) and of 1.0 for 1p-d\(_1\). A KIE of 1.3 was found for 1x-d\(_1\). The absence of significant KIE’s rules out breaking the C-H or [Ir-H]\(^\dagger\) bond in the rate-determining step (rds). This rules out mechanism C, for which a KIE is expected.\(^{19}\) Also, incorporation of deuterium at C\(_\alpha\) cannot occur through Mechanism C (2p-d\(_1\) in Scheme 4). In addition, the excellent
Mechanisms

Keywords: Allylic alcohol • Isomerization • Ir • EXAFS • Mechanism.

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Notes

† Authors contributed equally. 
‡ An inverse KIE was reported in Mechanism C. 
¥ B22 may still operate when the Ir–H is trapped within the solvent cage.


The first remarkably simple and general family of catalysts for isomerizing both primary and sec-allylic alcohols is reported. The catalysts, with the general structure [Cp*Ir(III)], only require to have a chloride or bromide ligand for optimal activity, as evidenced XAS and MS studies. No additional additive or ligand is needed. A mechanism is proposed based on kinetic investigations and isotopic labeling experiments.