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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 mask synthons 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,^[8] 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,^[4c,8] each catalyst isomerizes exclusively either primary or *sec*-alcohols efficiently. Each of these families trend to follow distinct isomerization mechanisms: whereas *sec*-alcohols form enone intermediates,^[1,5a,9] primary ones isomerize through migratory insertion/ β -hydride elimination

sequences.^[10-12] For the latter, transition-metal hydrides have given excellent results under mild conditions, enabling enantioselective isomerizations.^[4a,10-14]

We hereby report the isomerization of primary and secondary 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 $[\text{Cp}^*\text{Ir(III)}]$ complexes.^[3] 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 $[\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3]\text{SO}_4$ (**I**) and $[(\text{Cp}^*\text{Ir})_2(\text{OH})_3]\text{OH}$ (**II**),^[3c] without halogenating agent, **1a** was recovered (entries 1-4). In contrast, using $[\text{Cp}^*\text{IrCl}_2]_2$ (**III**) in THF or acetone/ H_2O mixtures, afforded **2a** in 85->99% in 30 min (entries 5-6).

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

[Cp*Ir(H ₂ O) ₃]SO ₄		[(Cp*Ir) ₂ (OH) ₃]OH		[Cp*IrCl ₂] ₂
	I	II	III	
Entry	Cat.	Solvent (v/v)	t (h)	Conv./Yield ^[a]
1	I	THF/H ₂ O (1:2)	16	-
2	I	Acetone/H ₂ O (2:1)	16	-
3	II	THF/H ₂ O (1:2)	16	-
4	II	Acetone/H ₂ O (2:1)	16	-
5	III	THF/H ₂ O (1:2)	0.5	85/85
6	III	Acetone/H ₂ O (2:1)	0.5	>99/97

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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 (**1t**) 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

Table 2. Scope.^a

[a] See SI. Yields by ¹H NMR, in parentheses isolated. [b] $[\text{Cp}^*\text{IrBr}_2]_2$ (IV). [c] III (0.5 mol%) >95%, 0.5 h. [d] ⁱPrOH, III (2.5 mol%), Ar at 100 °C (μ w). [e] From **Z-1aa**, 60 °C. [f] Degassed, 60 °C.

good yields. The *Z* conformer of allylic alcohol **1a** 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 *i*PrOH (SI), which resulted in excellent yields of hydromorphone (**7**) and hydrocodone (**8**) (Scheme 1). Interestingly, in pure *i*PrOH, analgesics dihydromorphone (**9**) and dihydrocodeine (**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%).

Scheme 1. Isomerization of opiates.

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%)^[3c] 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).^[3c]

Scheme 2. Isomerization of **1a** by **I** or **II** / **4**.

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 L_{III}-edge XAS was used to obtain further information about the local environment around Ir.^[17] The Ir L_{III}-edge X-ray absorption near edge structure spectroscopy (XANES) spectra of **II/4** and of [Cp*IrBr₂]₂ (**IV**) are similar. The position of the white line and the corresponding 2*p*-5*d* 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-C/Ir-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*IrBr₂]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 *in situ* form complexes of the general formula [Cp*IrBrX]_n, 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*IrBr₂]₂ (**IV**, Table 2).

Figure 1. Ir L_{III}-edge XANES (left) and Ir L_{III}-edge FT EXAFS (right) of **II**, **II/4**, and **IV**.

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 **11** and **1p**, and with primary **1x** and **1z**. Isomerization of **11-d₁** afforded **21-d₁**, with deuterium exclusively at C β (Scheme 4). In contrast, deuterium was found in both C α and C β in **2p-d₁**. For primary **1z-d₂**, deuterium was not detected at C α and one deuterium was exclusively transferred to C β (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 **11-d₁** and of 1.0 for **1p-d₁**. A KIE of 1.3 was found for **1x-d₁**. The absence of significant KIE's rules out breaking the C–H or [Ir–H]^[19] bond in the rate-determining step (rds). This rules out mechanism C, for which a KIE is expected.[†]^[20] Also, incorporation of deuterium at C α cannot occur through Mechanism C (**2p-d₁** in Scheme 4). In addition, the excellent

yields for both primary and *sec*-alcohols contrast with those reported in isomerizations through Mechanism C.^[18] The cross-over experiments rule out Mechanism A as well, since it necessarily involves non-bound [Ir–H] species, what would result in deuterium scrambling. The lack of reactivity of homoallylic **1h** also rules out path A.

To understand the different deuterium distribution in **2l** and **2p** (Scheme 4) variations in Mechanism B must be considered: a 1,4-hydride addition (B1) gives deuterium at C β . Alternatively, a change in coordination enables migratory insertion steps B2₁ and B2₂. Through the latter, deuterium can be incorporated at C α . For **1p** a combination of these three scenarios can account for the deuterium distribution. **1l** and **1z** may follow B1 or B2₁, or a combination. The lack of deuterium scrambling in all cases rules out pathway B2₃, *i.e.* de-coordination of [Ir–H] from the enone intermediate. In a mechanistic scenario through pathway B, the KIE experiments indicate that the rate limiting TS is located even before the C–H/D bond is broken, *i.e.* formation of the Ir–(allyl alkoxo) intermediate. Alternatively, the resting state is located after breaking of the C–H/D bond, and the rate-limiting TS is before the migratory insertion, *i.e.* the change in coordination from O– to olefin-bound enone.

In mixtures of acetone/*i*-PrOH (SI), evidence supporting Mechanism B was also obtained. Deuterium was detected in both C α and C β of the final ketones in the reaction of both **1p-d₁** and **1l-d₁**, suggesting participation of B2₁ and B2₂ pathways for both substrates.

In conclusion, we report a simple and general mild catalytic procedure for the isomerization of allylic alcohols. The protocol is based on the use of stable, and commercially available catalysts, and does not require the use of any ligand or additive. The reactions proceed in aqueous solvents, and can be run under air and at room temperature. Importantly, both primary and secondary allylic alcohols with different degrees of complexity can be isomerized. By XAS and MS studies we have demonstrated that the active catalyst must have at least one halide ligand. Mechanistic investigations support an oxidation/reduction pathway for all alcohols studied, with variations upon subtle changes in the reaction conditions and with the structure of the alcohols, despite using the same metal complex.

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

Notes

‡ Authors contributed equally.

† An inverse KIE was reported in Mechanism C.^[18]

¥ B2₃ may still operate when the Ir–H is trapped within the solvent cage.

¶ A brominating agent was used in the EXAFS studies instead of a chlorinating one. This is because being the Ir–Br bond distance larger than that of Ir–Cl, partial overlapping with the Ir–O/C band in the FT EXAFS is avoided.

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FULL PAPER

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.

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