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Homogeneous Catalysis

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 enable the isomerization of primary and *sec*-allylic alcohols under very mild reaction conditions. X-ray absorption spectroscopy (XAS) and mass spectrometry (MS) studies indicate that the catalysts, with the general formula [Cp*Ir^{III}], require a halide ligand for catalytic activity, but no additives or additional ligands are needed.

Isomerization reactions involving functional-group interconversions are highly important in organic synthesis. This is the case for transition metal-catalyzed isomerization of allylic alcohols.[1,2]Allylic alcohols are therefore masked synthons for preparing carbonyl compounds, including 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 the prior development of 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 was recently reported,[8] whereby a palladium hydride mediated the isomerization of primary and *sec*-allylic alcohols and remotely functionalized olefins. The established methods 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,[5a,8] each catalyst isomerizes exclusively either primary or *sec*-allylic alcohols efficiently, and tend 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 report here the isomerization of primary and *sec*-allylic alcohols by using remarkably simple, commercially available P/N-ligand-free Ir^{III} complexes. Allylic alcohols with mono-, di-, and trisubstituted double bonds were isomerized in aqueous solvents and even at room temperature and under an atmosphere of air. Insights into the structure of the active catalyst were obtained by mass spectrometry (MS) and X-ray absorption spectroscopy (XAS). Mechanistic investigations are also presented.

We have previously reported the synthesis of α-halocarbonyls from allylic alcohols catalyzed by [Cp*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 carried out the reactions of **1a** with catalysts **I**, **II**, and **III** (Table 1). Under the conditions previously used with [Cp*$Ir(H_2O)_3$]SO_4 (**I**) and [$(Cp^*Ir)_2(OH)_3$]OH (**II**),[3c] but without halogenating agent, unreacted **1a** was recovered (Table 1, entries 1–4). In contrast, the reaction with [{Cp*$IrCl_2$}$_2$] (**III**) in THF or acetone/H_2O mixture afforded **2a** in conversions of 85 and >99%, respectively, in 30 min (Table 1, entries 5 and 6).

The substrate 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,e,g**). The isomerization of olefin-functionalized **1f** indicated selectivity towards 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 iso-

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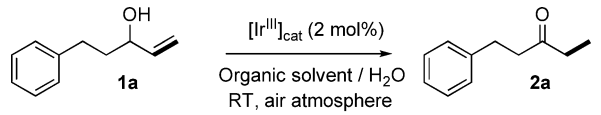
Table 1. Isomerization of **1a** by [Cp*Ir^{III}].



$[Cp^*Ir(H_2O)_3]SO_4$ $[(Cp^*Ir)_2(OH)_3]OH$ $[\{Cp^*IrCl_2\}_2]$

		I	II	III	
Entry	Cat.	Solvent (*v*/*v*)	*t* [h]	Conv. [%]	Yield [%][a]
1	**I**	THF/H_2O (1:2)	16	–	–
2	**I**	acetone/H_2O (2:1)	16	–	–
3	**II**	THF/H_2O (1:2)	16	–	–
4	**II**	acetone/H_2O (2:1)	16	–	–
5	**III**	THF/H_2O (1:2)	0.5	85	85
6	**III**	acetone/H_2O (2:1)	0.5	>99	97

[a] By ^{1}H NMR spectroscopy with internal standard.

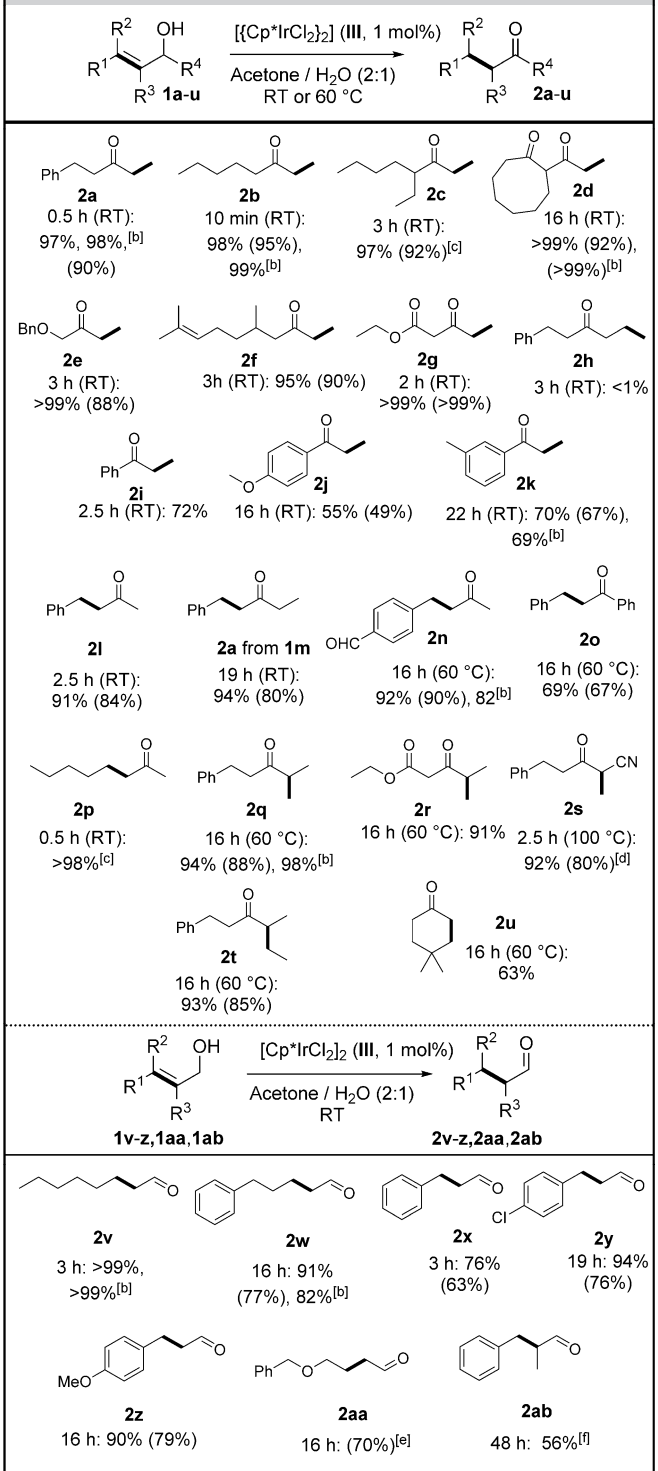
merized in excellent and moderate yields, respectively. *sec*-Allylic alcohols with 1,2,2-trisubstituted or tetrasubstituted double bonds did not isomerize. Interestingly, even primary allylic alcohols (**1v**–**z**) reacted smoothly at room temperature and the corresponding aldehydes **2v**–**z** were obtained in good yields. The *Z* conformer of allylic alcohol **1aa** was also converted 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] For reasons of solubility, H_2O was replaced by *i*PrOH (see the Supporting Information), which resulted in excellent yields of hydromorphone (**7**) and hydrocodone (**8**; Scheme 1). Interestingly, in pure *i*PrOH, analgesics dihydromorphine (**9**) and dihydrocodeine (**10**) were obtained from 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%)[3c] to the reactions shown in Table 1, entries 2 and 4, resulted in formation of isomerization product **2a** in 40 and 30% yield after 30 min, with **I** and **II** respectively (Scheme 2).[3c]

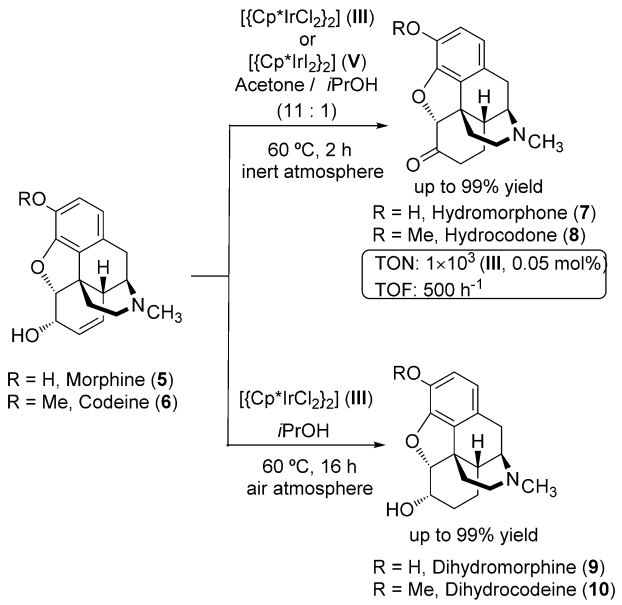
When complex **II** was treated with an excess of **4** (see the Supporting Information), an orange solid precipitated (labeled as **II**/**4**). By MS, the cation $[Cp^*IrBr]^+$ was identified (see the Supporting Information, Figure S5) and neither **I** nor **II** were detected. Ir L_{III}-edge XAS was used to obtain further information about the local environment around Ir.[17] The Ir L_{III}-edge X-ray absorption near-edge structure (XANES) spectra of **II**/**4** and of $[\{Cp^*IrBr_2\}_2]$ (**IV**) are similar. The position of the white line and the corresponding 2p–5d electronic transition is detected at around 11 214 eV (Figure 1, left). This energy is assigned to Ir^{III} with similar coordination environments.[17] The

Table 2. Substrate scope.[a]

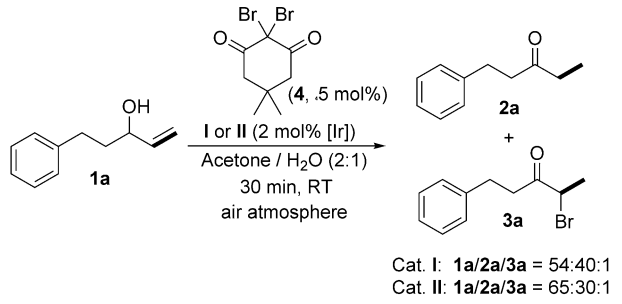


[a] See the Supporting Information; yields by ^{1}H NMR spectroscopy; values in parentheses refer to yields of isolated product; [b] $[\{Cp^*IrBr_2\}_2]$ (**IV**); [c] **III** (0.5 mol%), >95%, 0.5 h; [d] *i*PrOH, **III** (2.5 mol%), Ar at 100 °C (μw); [e] from *Z*-**1aa**, 60 °C; [f] degassed, 60 °C.

Fourier-transformed X-ray absorption fine structure (EXAFS) spectrum of **II**/**4** is dominated by peaks at $R \approx 1.76$ and 2.22 Å (without correcting for phase shifts and thus corresponding to actual distances of 2.13 and 2.55 Å), associated with Ir–C/Ir–O,



Scheme 1. Isomerization of opiates.



Scheme 2. Isomerization of **1a** by **I** or by **II** in the presence of **4**.

and Ir–Br interactions respectively; the peak linked to Ir–Br bonds was not found for **II** (Figure 1, right).[18]

The EXAFS data for **II**/**4** were fitted against a structural model based on the crystallographic data of **IV** and match with the presence of bridging bromides in this octahedral dimer (see the Supporting Information, Table S5). It can be concluded that **I** and **II** react with **4** to form complexes of the general formula $[\{Cp^*IrBrX\}_n]$ in situ, and that these are the catalytically active species, in accordance with the lack of activity of **I** and **II** in the isomerizations. This is supported by the excellent results also obtained with catalyst **IV** (Table 2).

We carried out mechanistic investigations to elucidate whether the reaction follows a migratory insertion/β-hydride elimination sequence (Scheme 3, mechanism **A**) or takes place via enone intermediates (Scheme 3, mechanism **B**). An alternative mechanism **C**, via π-allyl intermediates, was also considered.[19]

Isotopic labeling investigations were performed with *sec*-alcohols **1l** and **1p** and with primary alcohols **1x** and **1z**. Isomerization of $[D_1]$**1l** afforded $[D_1]$**2l**, with deuterium exclusively at Cβ (Scheme 4). In contrast, deuterium was found at both Cα and Cβ in $[D_1]$**2p**. For primary $[D_2]$**1z**, deuterium was not detected at Cα and one deuterium was exclusively transferred to Cβ (see the Supporting Information). In all cases, the deuterium content in the products corresponded well with that in the alcohols.

In a double crossover experiment, scrambling of deuterium between substrates did not occur for any type of alcohol (Scheme 5 and the Supporting Information).

A non-competitive KIE of 1.2 was determined for $[D_1]$**1l** and of 1.0 for $[D_1]$**1p**. A KIE of 1.3 was found for $[D_1]$**1x**. The absence of a significant KIE rules out breakage of the C–H or [Ir–H][20] bond in the rate-determining step (rds). This rules out mechanism **C**, for which a KIE is expected.[21] Moreover, incorporation of deuterium at Cα cannot occur through mechanism **C** ($[D_1]$**2p** in Scheme 4). In addition, the excellent yields for both primary and *sec*-alcohols contrast with those reported in isomerizations through mechanism **C**.[19] The crossover experiments also rule out mechanism **A**, since it necessarily involves non-bound [Ir–H] species, which would result in deu-

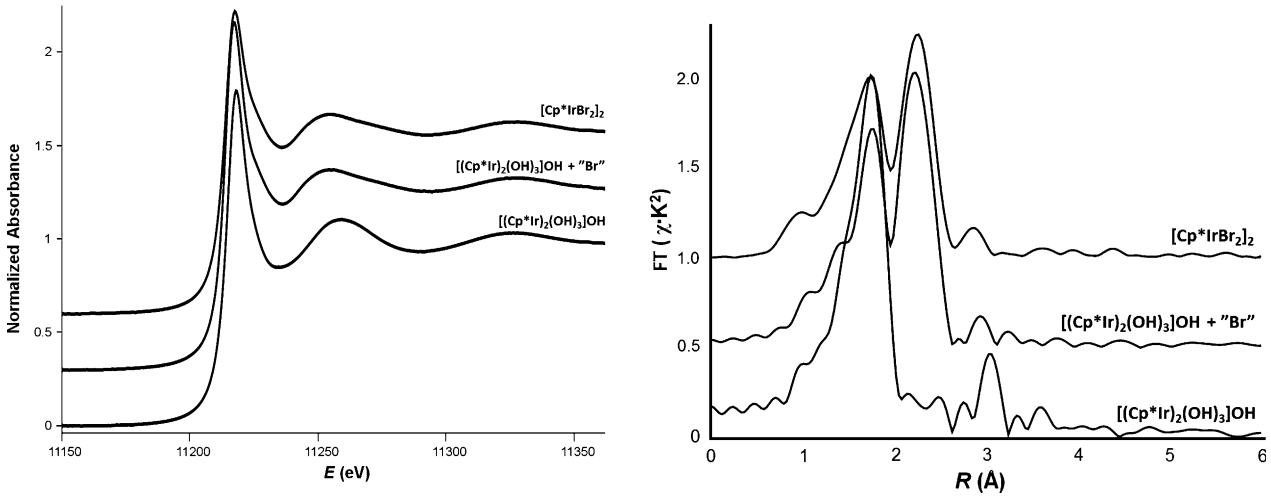
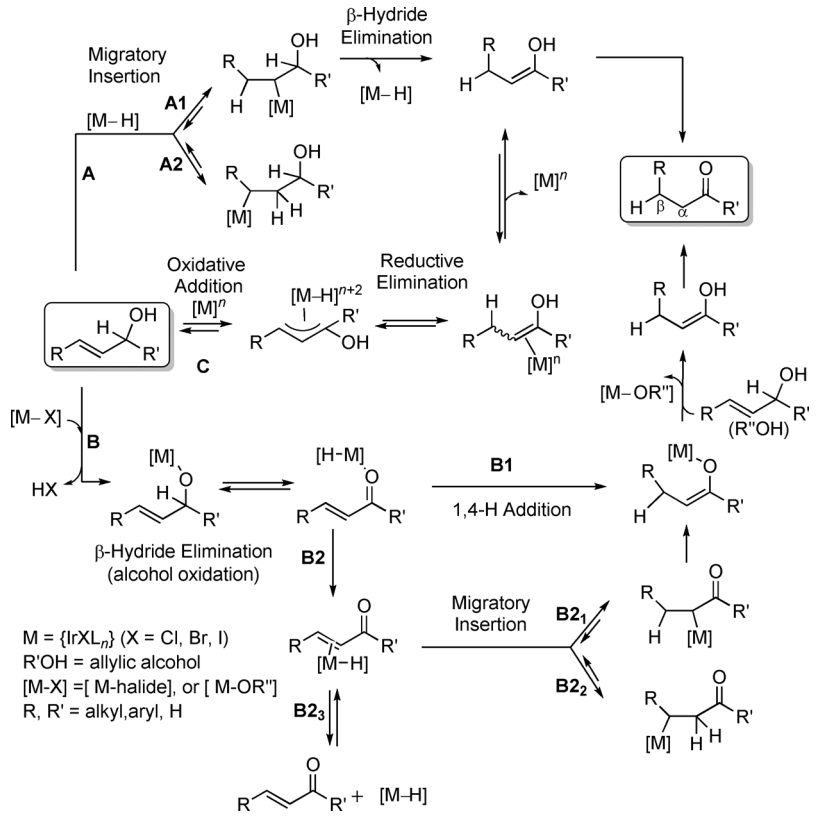
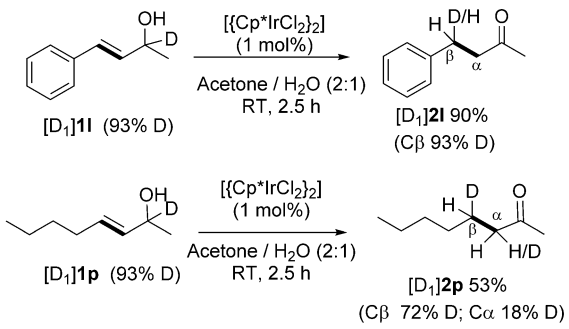


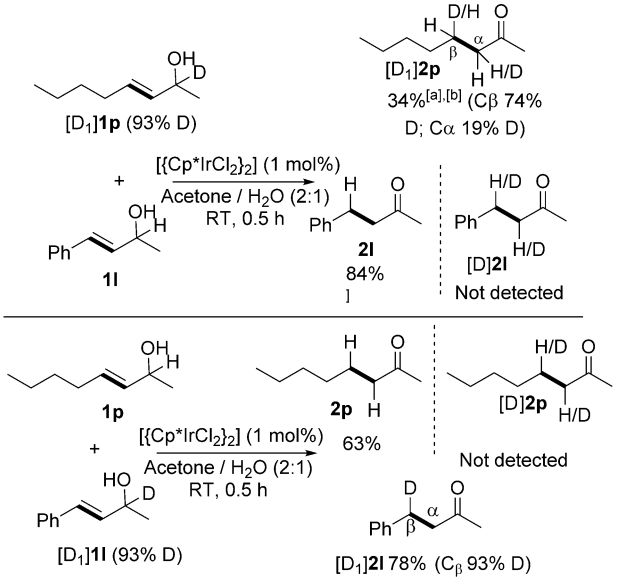
Figure 1. Ir L_{III}-edge XANES (left) and Ir L_{III}-edge FT EXAFS (right) spectra of **II** (bottom), **II**/**4** (middle), and **IV** (top).



Scheme 3. Proposed mechanistic scenarios.



Scheme 4. Deuterium labeling experiments.



Scheme 5. Crossover experiments.

terium scrambling. The lack of reactivity of homoallylic **1h** also rules out mechanism **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 Cβ. Alternatively, a change in coordination enables migratory insertion steps $\mathbf{B2_1}$ and $\mathbf{B2_2}$. Through the latter, deuterium can be incorporated at Cα. For **1p**, a combination of these three scenarios can account for the deuterium distribution. **1l** and **1z** may follow **B1** or $\mathbf{B2_1}$, or a combination thereof. The lack of deuterium scrambling in all cases rules out pathway $\mathbf{B2_3}$, that is, decoordination of [Ir–H] from the enone intermediate.[22] In a mechanistic scenario through mechanism **B**, the KIE experiments indicate that the rate-limiting TS is located even before the C–H/D bond is broken, that is, 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, that is, the change in coordination from O- to olefin-bound enone.

In mixtures of acetone and *i*PrOH (see the Supporting Information), evidence supporting mechanism **B** was also obtained. Deuterium was detected at both Cα and Cβ of the final ke-

tones in the reactions of both [D_1]**1p** and [D_1]**1l**, suggesting participation of $\mathbf{B2_1}$ and $\mathbf{B2_2}$ pathways for both substrates.

In conclusion, we have reported a simple and general mild catalytic procedure for the isomerization of allylic alcohols. The method is based on the use of stable, commercially available catalyst and does not require the use of any ligand or additive. The reactions proceeded in aqueous solvents, and could be run under air and at room temperature. Importantly, both primary and secondary allylic alcohols with different degrees of complexity were isomerized. By XAS and MS studies, we demonstrated that the active catalyst must have at least one halide ligand. Mechanistic investigations supported 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 alcohols · X-ray absorption spectroscopy · isomerization · iridium · reaction mechanisms

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[22] Note that $\mathbf{B2_3}$ may still operate when the Ir–H is trapped within the solvent cage.

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Homogeneous Catalysis

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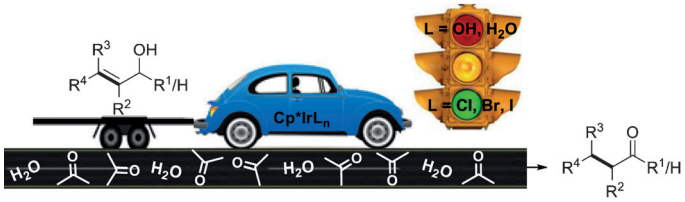

The allylic job: A remarkably simple and general family of catalysts for isomerizing both primary and *sec*-allylic alcohols is reported. The catalysts, with the general formula [Cp*Ir^{III}], only require a halide ligand for optimal activity, with no additional additive or ligand needed. A mechanism is proposed based on kinetic investigations and isotopic labeling experiments.