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Iridium-catalyzed isomerization of primary allylic alcohols under mild reaction conditions

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ABSTRACT

The isomerization of primary allylic alcohols into the corresponding aldehydes has been accomplished using an analogue of Crabtree's iridium hydrogenation catalyst and by adequately tuning the experimental conditions. A wide range of substrates is converted quantitatively into the desired aldehyde at room temperature in expedient reaction times by using catalyst loading as low as 0.25 mol %.

The isomerization of primary and secondary allylic alcohols to the corresponding aldehydes and ketones is a reaction of great synthetic value.[1] We are particularly interested in the former transformation because of the high versatility of aldehydes. As of today, there is no general and practical catalyst that functions under mild reaction conditions and displays a wide substrate generality, in particular for less reactive primary allylic alcohols with sterically hindered and/or highly substituted olefins.[1,2] In transition metal-catalyzed hydrogenation reactions, isomerization of olefins is the most common competing process that is usually hampered by either increasing the hydrogen pressure or by adequately tuning the steric and electronic properties of the surrounding ligands.[3] Inspired by Baudry and Ephritikhine work,[4] we initially reasoned that under appropriate experimental conditions selected hydrogenation catalysts may preferentially follow a productive isomerization pathway rather than the hydrogenation route.[2] We report here the identification of a highly active catalyst promoting the isomerization of a wide range of primary allylic alcohols under very mild reaction conditions.

In the late 1970s, Crabtree has described that the cationic iridium complex $[Ir(PCy_3)(pyridine)(COD)]PF_6$ **1** (COD = 1,5-cyclooctadiene) is effective for the hydrogenation of highly substituted unfunctionalized alkenes.[5] In 1983, Stork[6] and Crabtree[7] have convincingly demonstrated that the hydroxyl group plays a crucial directing role in the reduction of cumbersome allylic alcohols and homoallylic alcohols using the same catalyst. Previous attempts to use **1** in isomerization reactions have proven elusive since the high loadings usually employed (10–20 mol %) were accompanied by reproducibility[4] and selectivity[8] issues. Related iridium catalysts have been shown to promote the isomerization of allylic alcohols. Nevertheless, mild conditions are only appropriate for few disubstituted allylic alcohols. In addition, side reactions often accompany the desired isomerization process.[3b,4,9] In hydrogenation reactions, the bulky, highly lipophilic, BAr_F^- ($B[(3,5\text{-}(CF_3)_2)C_6H_3)_4]^-$) counter-anion was shown to favor olefin coordination and to slow down deactivation due to very weak and non-competitive ion-pairing interactions.[10,11] Superior catalytic performances of **2** over **1** in hydrogenation reactions have been independently reported by Buriak[10c] and Pfaltz.[10e]

Preliminary investigations started with a comparative study of catalysts **1** and **2**. As anticipated, the experimental set-up of the isomerization reactions turned out to be crucial. Activation of the cyclooctadiene precatalysts was performed by bubbling molecular hydrogen directly through the solution and followed by two freeze–pump–thaw cycles to exclude the excess of hydrogen gas from the reaction media prior to substrate addition.[12] Reactions were carried out in THF at room temperature using 5 mol % of precatalyst and (*E*)-4-methyl-3-phenyl-2-pentenol as model substrate (Scheme 1). Whereas Crabtree catalyst analogue **2** afforded the aldehyde quantitatively with no traces of the saturated alcohol, the original Crabtree catalyst **1** gave only 74% of the expected product.[13] Other potent iridium hydrogenation catalysts **3–7** of general formula $[Ir(L^1)(L^2)(COD)]BAr_F$ were also evaluated in the isomerization reaction.[14] Surprisingly, none of these complexes afforded the desired aldehyde using the same experimental protocol. Although we do not have yet a rationale for this observation, this striking result indicates that any variation of the electronic or

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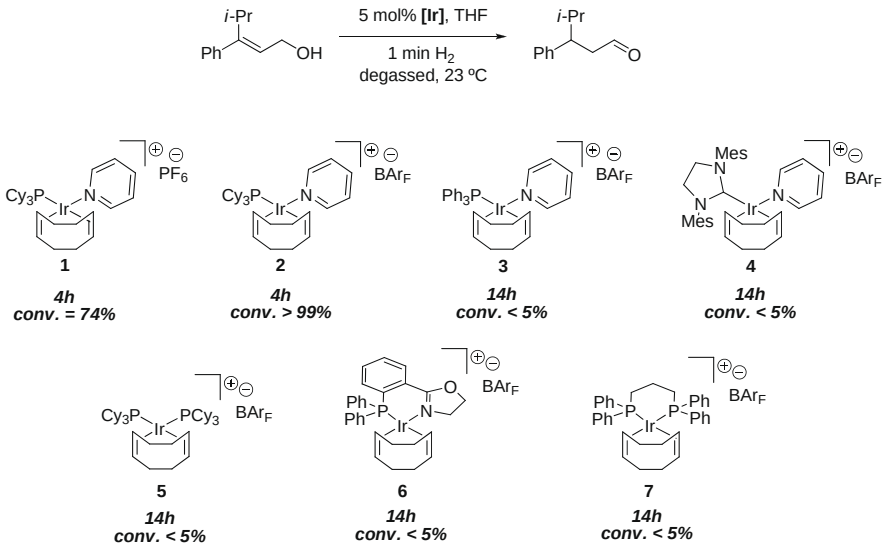


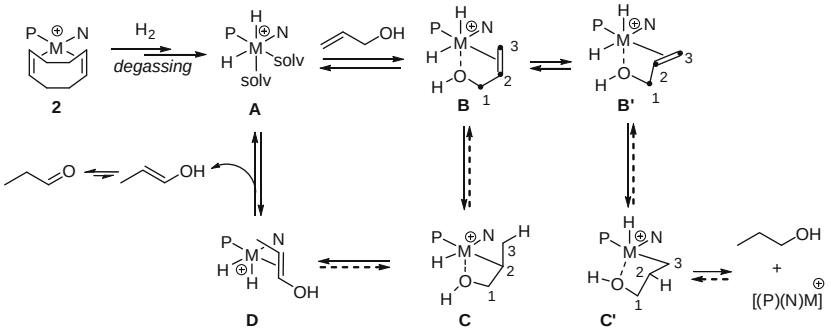
Scheme 1. Survey of iridium catalyst in the isomerization of primary allylic alcohol.

steric properties of complex **2** leads to a complete loss in activity. The scope of the isomerization reaction using catalyst **2** was investigated next (Table 1). 3,3-Dialkyl-substituted aldehydes were obtained from the corresponding allylic alcohols using low catalyst loadings (0.25–1.0 mol %) in very short reaction time (entries 1–4). Using 5 mol % of **2** for the isomerization of the sterically more demanding (*E*)-3,4,4-trimethylpent-2-enol afforded quantitatively the desired product within 16 h (entry 5). Despite a conjugated system, cinnamyl alcohol and related electron-rich heterocycles also reacted under very mild conditions (entries 6, 14, and 15). Less reactive analogues bearing an additional 3-alkyl substituent required slightly increased amount of catalyst as well as reaction time to undergo complete conversion (entries 7–11).

Substrates with a 2,3-substitution pattern reacted in a contrasted manner, presumably reflecting the relative stability of the enols. Whereas a methyl group on the 2-position allows expedient access to the expected α-substituted aldehyde, a phenyl ring considerably decelerates the reaction and requires higher loadings of catalyst (entries 12 and 13). Finally, under more forcing conditions (10 mol % of **2**, 65 °C), an allylic alcohol with a tetrasubstituted olefin was converted to a 1:1 mixture of cis and trans isomerization products (entry 16). Attempts to isomerize secondary allylic alcohols under the same reaction conditions have proven unsuccessful so far. Activation of C_1-symmetric (P,N)-iridium complexes by molecular hydrogen generates intermediates of type **A** where both hydrides are located cis to the P atom (Scheme 2).[5,14–16]

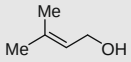
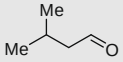
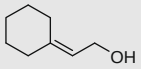
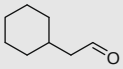
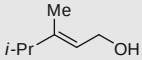
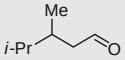
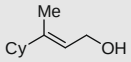
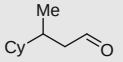
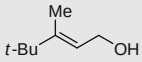
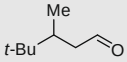
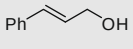
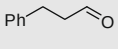
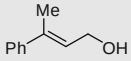
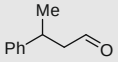
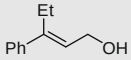
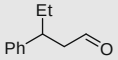
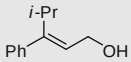
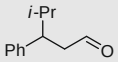
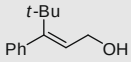
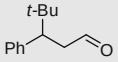
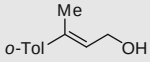
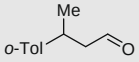
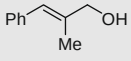
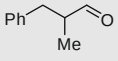
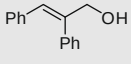
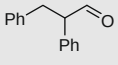
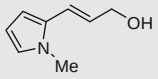
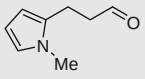
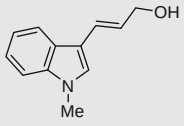
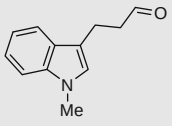
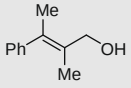
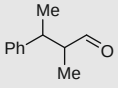
According to our initial hypothesis, discrimination between hydrogenation and isomerization pathways is expected to arise from intermediates **B** and **B'** depending whether migratory insertion occurs preferentially at C(2) or at C(3), respectively. Labeling experiments using 1,1-dideuterated model substrate and variable loadings of complex **2** were carried out under standard conditions (Fig. 1).

In each case, along with dideuterated aldehyde, monodeuterated aldehyde, indicative of an intermolecular process, was unequivocally observed by EI-HRMS. Since only one hydride is stereoelectronically aligned with the $\sigma^*_{C=C}$ to undergo migratory insertion, complete transfer of hydrogen to the product implicates rapid exchange between the two hydrides in **A**. Furthermore, ^{1}H NMR analysis of the crude reaction mixtures recorded after complete conversion showed that exclusive incorporation of hydrogen at C(3) was twice proportional to the initial loading in **2**. This was further confirmed by 2D ROESY experiments measured in the hydride region (−15 to −35 ppm) after generating [**A**]BAr_F in THF-d_8 and degassing.[11] In addition, if the substrate coordinates via both the olefin and the hydroxyl group as demonstrated by Stork[6] and Crabtree[7] in their hydrogenation studies, the binding of the alcohol must be reversible to allow β-H(1)-elimination in the isomerization pathway (**C**→**D**, Scheme 2). Consistent with our mechanistic hypothesis, an energetically too demanding β-H-elimination step may be ascribed to the absence of reactivity of **2** toward secondary allylic alcohols.



Scheme 2. Proposed catalytic cycle.

Table 1
Substrate scope for the isomerization of allylic alcohol using **2**

Entry[a]	Substrate	Product	**2** (mol %)	Time (h)	Conversion[b] (%)
1			0.25	0.5	>99
2			0.25	0.5	>99
3			1	0.5	>99
4			0.25	2	95[c]
5			5	16	>99
6			0.5	1	>99
7			2	4	>99[c]
8			1	6	98
9			1	4	>99[c]
10			5	2	>99
11			2	4	>99
12			0.5	1	>99
13			5	22	95
14			1	2	98
15			1	2	>99
16			10	22	98[d]

[a] Average of at least two runs on a 0.2 mmol scale e.
[b] Determined by ^{1}H NMR. Separation of the deactivated catalyst was accomplished by filtration through a short plug of silica leading to nearly quantitative yields in all cases.
[c] Identical results are obtained starting from the (*Z*)-isomer.
[d] A 1:1 mixture of trans/cis diastereoisomers was obtained.

In summary, we have designed an experimental protocol that revealed the ability of Crabtree catalyst analogue **2** to promote cleanly the isomerization of a wide range of primary allylic alcohols in the corresponding aldehydes. Reactions were run at room temperature with appreciable reaction rates using low catalyst loadings (0.25–5.0 mol %). Unprecedented isomerization of a primary allylic alcohol with a tetrasubstituted olefin was achieved using higher catalyst loading and temperature.

Our initial mechanistic hypothesis has been supported by preliminary investigations. The catalyst stability and accessibility as well as the generality of the process and the mild reaction conditions may hold promise for widespread use of this method.

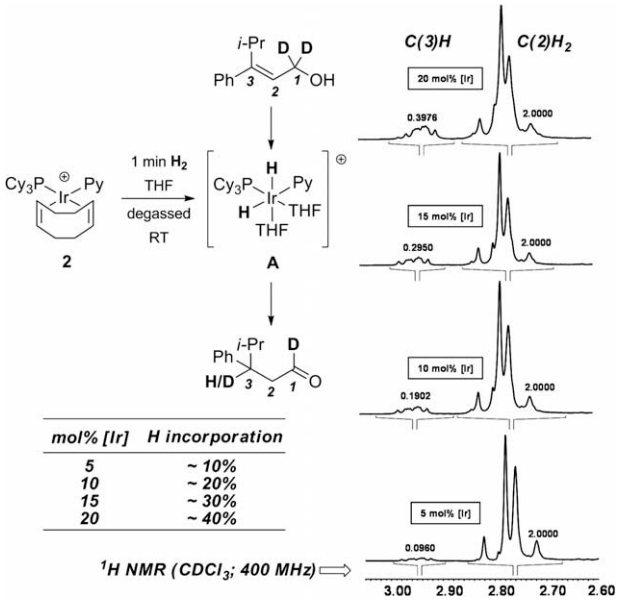


Figure 1. Labeling experiments using 1,1-dideuterated model substrate. The NMR overlay shows the relative integration between C(3)H and C(2)H_2 for all four experiments.

Acknowledgments

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16. For identification of iridium-dihydride intermediate **A**, see Supplementary data.