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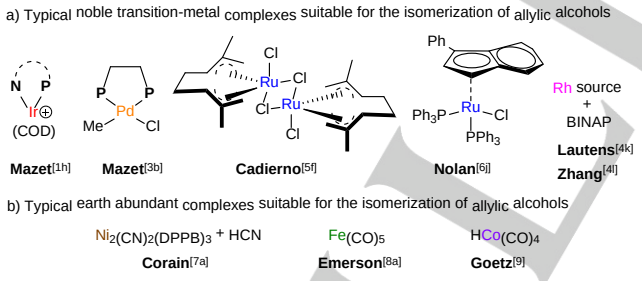
# Isomerization of Allylic Alcohols to Ketones Catalyzed by well-defined Iron PNP Pincer Catalysts

Tian Xia[+], Zhihong Wei[+], Brian Spiegelberg, Haijun Jiao, Sandra Hinze and Johannes G. de Vries*

**Abstract:** Fe(PNP)(CO)HCl (PNP = di-(2-diisopropylphosphanyl-ethyl)amine), activated *in situ* with KO*t*Bu, is a highly active catalyst for the isomerization of allylic alcohols to ketones without external hydrogen supply. High rates were obtained at 80 °C but the catalyst is also sufficiently active at room temperature with most substrates. The reaction follows a self-hydrogen-borrowing mechanism as verified by DFT calculations. An alternative isomerization via alkene insertion and beta-hydride elimination could be excluded on the basis of the much higher barrier. In alcoholic solvents, the product ketone is further reduced to the saturated alcohol.

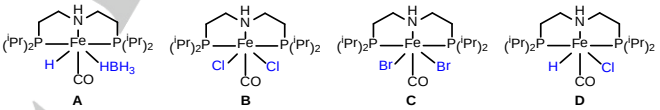
## Introduction

The catalytic isomerization of allylic alcohols to carbonyl compounds, such as ketones and aldehydes, is 100% atom economic and has been widely used in organic synthesis. Unlike the classic two-step oxidation-reduction sequence or the reverse, the isomerization reaction is green, efficient and clean as well as environmentally sustainable and proceeds in one-step without producing any by-products and without requiring toxic reagents.[1] Various noble transition metal complexes, based on iridium,[2] palladium,[3] rhodium,[4] and ruthenium,[5],[6] are known to catalyze the isomerization of allylic alcohols in very high yields and with excellent turnover numbers (Scheme 1a).




**Scheme 1.** Transition-metal complexes for the isomerization of allylic alcohols

The development of catalysts based on earth abundant metals like nickel[7], iron[8], or cobalt[9] for isomerization reactions is an emerging research area. The first example of a nickel catalyzed isomerization reaction of allylic alcohols was reported by Corain,[7a, b] who utilized a combination of $Ni(DPPB)_2$/HX (HX = HCN, $CF_3COOH$, $CCl_3COOH$, and $H_2SO_4$) (Scheme 1b). Later, similar acid activated nickel systems were described.[7e] Iron carbonyl compounds were also employed successfully, delivering acceptable yields and turnover frequencies (TOF, up to 95 $h^{-1}$).[8g] However, the major drawback of these iron carbonyl complexes is the necessity to use UV light for their activation as well as their toxicity. Hence, they cannot be used for large scale production. Therefore, new low-cost iron-based catalysts that are not toxic and do not need UV light are urgently needed. To the best of our knowledge, there is only one report[10] on the use of an ill-defined iron(II) compound for the isomerization of allylic alcohols, which requires one equivalent of base and a trifluoro-methyl moiety in the substrates. Herein, we report the first iso-merization of non-activated allylic alcohols catalyzed by pincer PNP-iron (II) complexes. A range of different substrates were tested with these novel catalysts and high TOFs were achieved.




**Scheme 2.** PNP-Iron complexes (**A**-**D**) applied in the isomerization of non-activated allylic alcohols in this work

## Results and Discussion

In recent years, pincer-ligated iron complexes have been used for hydrogenation reactions.[11] The groups of Schneider,[11g] Guan[12] and Beller[13] independently reported the synthesis of iron compound **A** (Scheme 2) which is a decent catalyst for the hydrogenation of esters,[12-14] nitriles[15] and heterocycles.[16] Intrigued by this, we assumed that this and similar iron catalysts might also be suitable for isomerization reactions and tested them in the isomerization of oct-1-en-3-ol (**1**) to 3-octanone (**2**). Initial tests were performed in isopropanol at 80 °C (Table 1, full screening of catalysts in the supporting information). Traces of product were formed in the presence of catalyst **A** (Entry 1). It is known that bases play an important role in catalyst activation. Indeed, adding 2 mol% of potassium *tert*-butoxide resulted in 90% conversion, albeit with low selectivity to the desired product (Entry 2). Catalysts **B** and **C** turned out to be inactive even at catalyst loadings of 2 mol% and addition of 4 mol% $^t$BuOK (Entries 3 and 4). Under the same conditions catalyst **D** gave full conversion, yet again with poor selectivity towards the desired ketone **2** (Entry 5). Reducing the amount of catalyst and reaction

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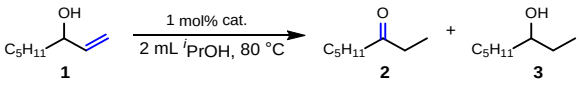
**Table 1**. Catalyst screening in allyl alcohol isomerization [a]




1 2 3

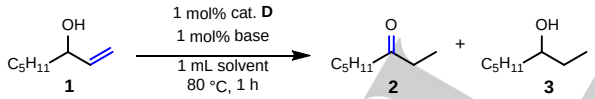
| Entry | Cat. | Time [h] | Conv. **1** [%][b] | **2** [%][b] | **3** [%][b] |
|---|---|---|---|---|---|
| 1 | **A** | 15 | trace | trace | trace |
| 2[c] | **A** | 15 | 90 | 28 | 60 |
| 3[d] | **B** | 24 | 0 | 0 | 0 |
| 4[d] | **C** | 24 | 0 | 0 | 0 |
| 5[d] | **D** | 24 | 99 | 9 | 90 |
| 6[c] | **D** | 24 | 99 | 11 | 88 |
| 7[c] | **D** | 3 | 100 | 15 | 84 |

[a] 1 mmol substrate. [b] Determined by GC with dodecane as internal standard. [c] 2 mol% of tBuOK. [d] 2 mol% catalyst, 4 mol% tBuOK. [e] 1 mol% of tBuOK w.r.t. to substrate.

time did not change this output significantly (Entries 6 and 7). This preliminary investigation showed that catalyst **D** was unsurpassed for good conversion. In addition, this compound is stable for at least 6 months in the glovebox.

Next, the effect of solvent and base on the reaction selectivity was investigated. Utilization of ethanol resulted in lower conversion and yield (Table 2, Entries 1 and 2). THF is a commonly used solvent in isomerization reactions and delivered high conversion as well as high selectivity towards the desired ketone **2** (Entry 3). Full conversion was also observed using toluene and benzene as solvent (Entries 4-6, respectively). In contrast, use of acetonitrile resulted in low conversion and selectivity (Entry 7). A limited number of other bases were also screened. Compared to potassium *tert*-butoxide, sodium and lithium *tert*-butoxide resulted in lower conversion and selectivity (Entries 8 and 9). No conversion was obtained with potassium carbonate (Entry 10).

**Table 2.** Solvent and base screening in allylic alcohol isomerization.[a]




1 2 3

| Entry | Base | Solvent | Conv. **1** [%][b] | **2** [%][b] | **3** [%][b] |
|---|---|---|---|---|---|
| 1[c] | $^t$BuOK | *i*PrOH | 100 | 15 | 84 |
| 2[c] | $^t$BuOK | EtOH | 60 | 31 | 29 |
| 3[c] | $^t$BuOK | THF | 98 | 96 | 2 |
| 4[c] | $^t$BuOK | Toluene | 100 | 99 | 1 |
| **5** | **$^t$BuOK** | **Toluene** | **100** | **98** | **2** |
| 6 | $^t$BuOK | Benzene | 100 | 99 | trace |
| 7 | $^t$BuOK | $CH_3CN$ | 33 | 33 | 0 |
| 8[d] | $^t$BuONa | THF | 85 | 79 | 5 |
| 9[d] | $^t$BuOLi | THF | 43 | 39 | 3 |
| 10 | $Na_2CO_3$ | Toluene | 0 | 0 | 0 |

[a] 1 mmol substrate. [b] Determined by GC with dodecane as internal standard. [c] Reaction time 3 hours. [d] Reaction time 1.5 hours. [e] Isolated yield under neat conditions on 10 mmol scale for 2 hours.

Taking efficiency, toxicity and price into account, either toluene or THF can be used as solvent and potassium *tert*-butoxide was selected as base in all further experiments (further screening experiments can be found in the Supporting Information). Under the optimized conditions (Entry 5), we measured the conversion of **1**, taking samples every 2 minutes (See Supporting Information); full conversion was achieved in 20 minutes at room temperature as well as in 6 minutes at 80 °C (Figure 1).

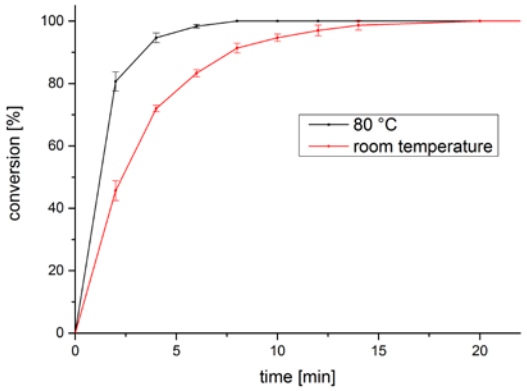
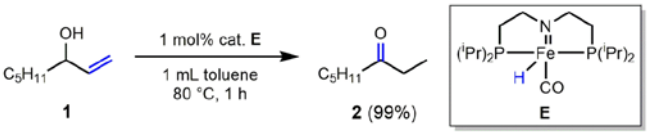



**Figure 1.** Monitoring the isomerization reaction over time: 1 mmol oct-1-en-3-ol, 1 mol% catalyst D, 1 mol% of tBuOK, 1 mL D-toluene, monitored by 1H-NMR. Data given are averaged conversions of three reactions.

In order to explore the mechanism of the isomerization reaction, we synthesized the amido complex **E** (Scheme 3) according to the protocol reported by Jones[16] and Schneider,[17] starting from iron complex **D** (Scheme 2) by deprotonation with $^t$BuOK. When complex **E** was applied to the isomerization of **1**, the desired ketone (**2**) was obtained in 99% yield.




1 2 (99%) E

**Scheme 3.** Experiments with presumed catalytically active species E

To test the scope and limitations of this catalyst system a range of substituted allylic alcohols bearing an aromatic (Scheme 4, **2a-2l**) or an aliphatic (**2m-2n**) substituent $R^2$ was tested under the optimized reaction conditions (Table 2, Entry 6). Excellent yields of the ketones were obtained with substrates containing electron-donating and electron-withdrawing groups on the aromatic ring (**2a** to **2e**). Substrate **1f** bearing a naphthyl substituent also led to outstanding results (**2f**). The heterocyclic furanyl and thienyl substituted substrates were converted to the corresponding ketones **2g** and **2h** with satisfying isolated yields. Substituents ($R^1$) on the C=C double bond had no detrimental effect on the conversion. Smooth conversion of **1k** to **2k** shows that a benzylic alcohol is not a prerequisite for this isomerization. Interestingly, homo-allylic alcohol **1l** was also isomerized to the

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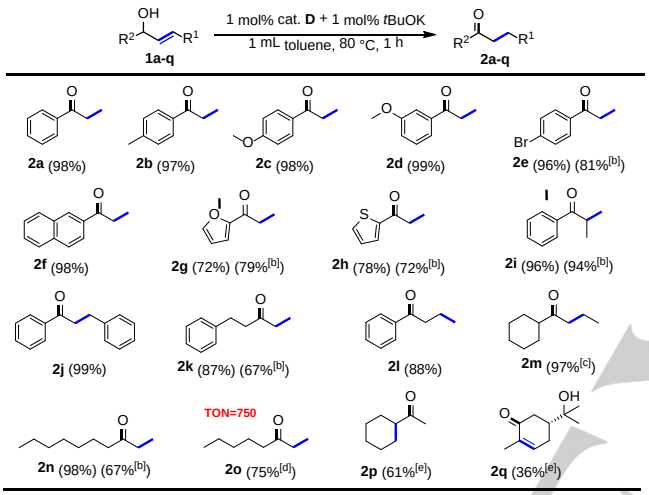
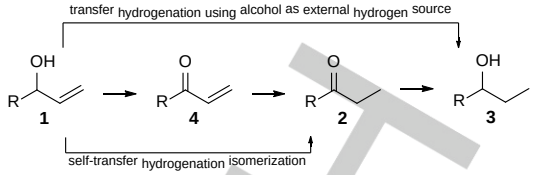
desired ketone **2l**. The protocol was also applied successfully to aliphatic allylic alcohols (**2m** to **2o**). Aliphatic substrate **2m** with an internal double bond was also isomerized in good yield. The isomerization can also be performed at room temperature resulting in high yields within two hours (**2e**, **2g**, **2h**, **2i**, **2k**, **2n**), as well as under neat conditions at 80 °C for two hours (**2o**). The cyclic allylic alcohol 1-cyclohexene-1-yl-ethanol was converted to (**2p**) in 61% yield. Interestingly, *trans*-sobrerol only underwent dehydrogenation to form the unsaturated ketone (**2q**), which is presumably caused by the steric hindrance of the extra methyl group, which hinders the alkene hydrogenation.

**Scheme 4.** Substrate scope of iron-catalyzed allylic alcohol isomerization[a]




[a] 1 mmol substrate, isolated yields, bold blue bond is the position of the original C=C bond in the substrates. [b] Room temperature, t = 2h [c] Substrate is a mixture of *cis* and *trans*. [d] Neat conditions on 10 mmol scale, 0.1 mol% catalyst, t = 2 h. [e] t = 16 h, 5 mol% catalyst D, 5 mol% *t*BuOK.

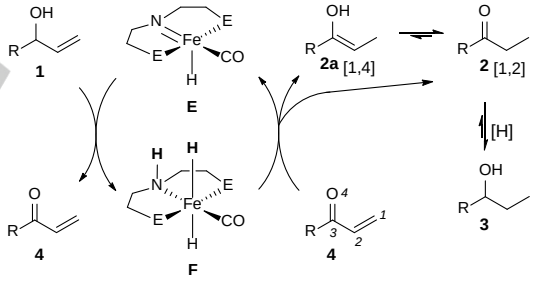
These results show two interesting mechanistic aspects. As shown in Scheme 5, the first one is the isomerization for which we propose a mechanism *via* self-transfer hydrogenation, where allylic alcohol **1** will be first dehydrogenated into α,β-unsaturated ketone **4**, which can be further hydrogenated into ketone **2**; and this can be seen for the reactions in benzene or toluene solution (Table 2, entries 4-6) and the major product is the isomerized ketone **2**. The second one is the transfer hydrogenation using alcohols such as ethanol or isopropanol as solvent and hydrogen source, where allyl alcohol **1** will be either directly transfer hydrogenated into the saturated alcohol **3** as the major product (Table 1, entries 5 and 6; as well as Table 2, entry 1); or the isomerized ketone **2** is reduced via transfer hydrogenation to the alcohol **3**. The formation of ketone **2** as minor product in these reactions in alcohols indicates that both self-transfer hydrogenation isomerization and transfer hydrogenation using alcohol as hydrogen source might occur simultaneously on the basis of the kinetic and thermodynamic properties.




**Scheme 5.** Proposed reaction routes

To gain a better mechanistic understanding, B3PW91 DFT computations were performed. The applicability of the B3PW91 functional was validated intensively and extensively.[18] In our previous work we have done intensive and extensive testing and benchmarking of different methods with and without solvation effect and dispersion as well as intensive comparisons with the available experimental data and computational data for different transition metal PNP type complexes (M = Fe, Ru, Os, Ir, Mn, Mo and W).[19] On the basis of these tests and comparisons, we find full agreement between theory and experiment, which validates the B3PW91 gas phase calculation as reasonable. All computational details are given in the Supporting Information.

In view of the need for a strong base for complex **D** to function as catalyst as well as the catalytic activity of complex **E** without strong base, we first computed the self-transfer hydrogenation isomerization of **1** to **2** based on an outer-sphere mechanism without external hydrogen source, starting from complex **E** as shown in Scheme 6. The full potential energy surface is shown in Scheme 7.




**Scheme 6**. Proposed mechanism (R = $C_5H_{11}$, E = $P(^iPr)_2$)

Without external hydrogen supply, the first step is the dehydrogenation of **1** to **4** by complex **E**. Here the first step is hydride transfer from the alcohol to Fe. It is found that the transition state corresponding to hydride transfer has a Gibbs free energy barrier of 92.1 kJ/mol and the reaction is endergonic by 5.0 kJ/mol. As hydride transfer was proven to be the rate-determining step for C=O bond hydrogenation on Fe as well as on Mn and $d^5$-, $d^6$- metal PNP pincer complexes,[19c, 20] we assume that the energy barrier of dehydrogenation of **1** to **4** is determined by the hydride transfer. Although great efforts have been made, the transition state corresponding to proton transfer as well as the $PN^HP$-$Fe^+$−RCH($O^-$)CH=$CH_2$ intermediate could not be located and all attempts to optimize such structures resulted in reactant or transition state of hydride transfer.

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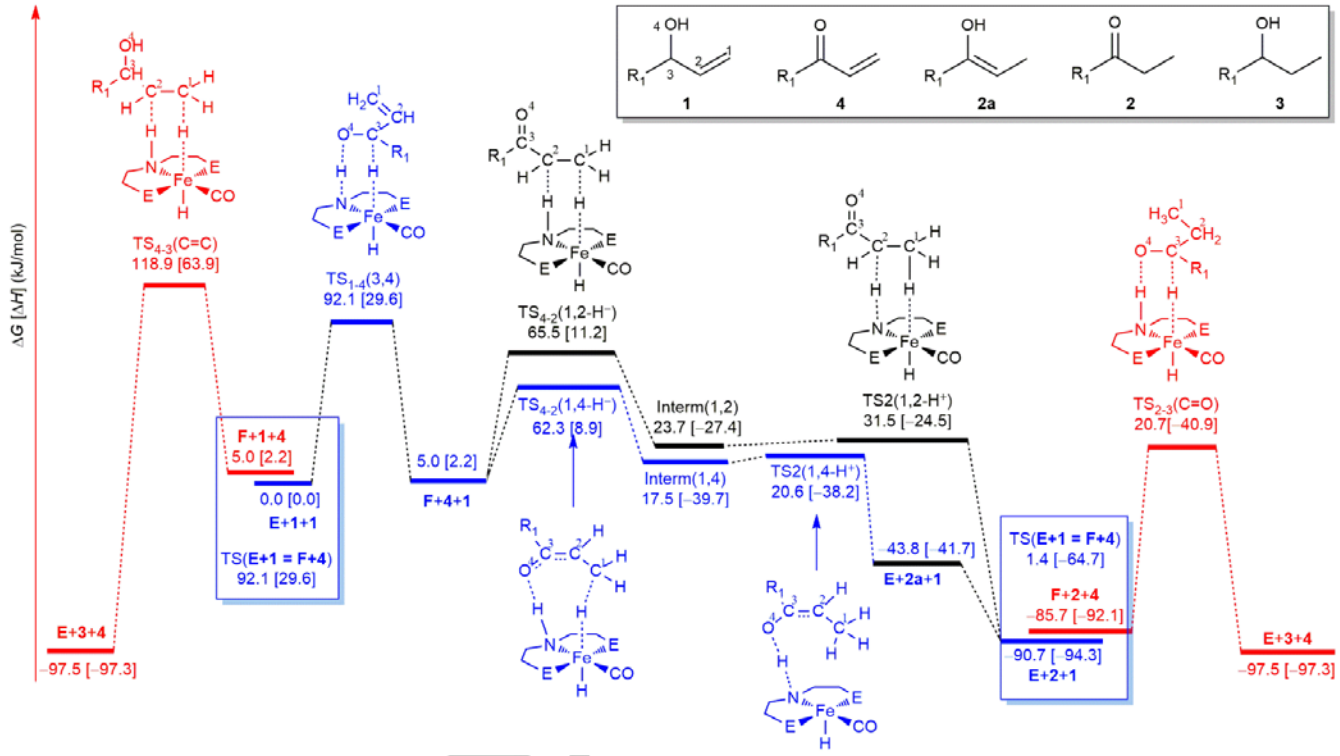
The next step is the hydrogenation of the C=C bond from the newly formed **4** to **2** by complex **F** *via* either 1,2-addition directly to **2** or *via* 1,4-addition to form the enol **2a**, which can tautomerize into **2**. For the 1,2-addition, we found a stepwise mechanism; i.e.; the first step passes through the transition state for Fe−H transfer to $C_1$, by breaking the Fe−H bond and forming the C-H bond, leading to an intermediate. The second step passes through the transition state of N−H transfer to $C_2$ by breaking the N−H bond and forming the terminal $C_1$−H bond. For the 1,2-addition, the free energy barrier of the Fe−H hydride transfer is 60.5 kJ/mol, the intermediate is endergonic by 18.7 kJ/mol, and the N−H proton transfer has a free energy barrier of 26.5 kJ/mol. This hydrogenation step is exergonic by 95.7 kJ/mol.

For the 1,4-addition, we also found a stepwise mechanism; i.e.; the first step passes through the transition state for Fe−H transfer to the $C_1$ by breaking the Fe−H bond and forming the C−H bond, leading to an intermediate. The second step passes through the transition state of N−H transfer to the $O_4$ by breaking the N−H bond and forming the terminal O−H bond. From the starting point for 1,4-addition, the free energy barrier of the Fe−H hydride transfer is 57.3 kJ/mol, the intermediate is endergonic by 12.5 kJ/mol, and the N−H proton transfer has a free energy barrier of 15.6 kJ/mol. This hydrogenation step is exergonic by 48.8 kJ/mol. The tautomerization from **2a** to **2** is exergonic by 46.9 kJ/mol. The overall isomerization from **1** to **2** is exergonic by 90.7 kJ/mol. This indicates that 1,4-addition is slightly more favored kinetically than 1,2-addition by 3.2 kJ/mol; and this small energy difference shows that both the 1,2- and 1,4-routes are competitive and possible.




**Scheme 7.** Reaction profile for the isomerization of **1** to **2** ($R_1 = C_5H_{11}$, E = P(*i*Pr)$_2$)

This shows that the hydrogenation of **4** to product **2** is more favored kinetically (57.3 vs. 92.1 kJ/mol) and thermodynamically (-95.7 vs. 5.0 kJ/mol) than the dehydrogenation of **1** to **4**. Therefore, **4** once formed, can be easily converted to **2**.

In addition, we computed the competitive hydrogenation of **1** to **3** by using complex **F** after the dehydrogenation of one equivalent **1** into **4**. The hydrogenation of **1** to **3** proceeds *via* a one-step mechanism mainly corresponding to the hydride transfer and is exergonic by 102.5 kJ/mol and the barrier is 113.9 kJ/mol, indicating that the isolated C=C double bond hydrogenation of **1** is less competitive kinetically than the conjugated C=C double bond hydrogenation of **4** by 56.6 kJ/mol. Furthermore, we also computed the consecutive hydrogenation of **2** to **3** by using complex **F** after the dehydrogenation of another one equivalent **1** into **4**. We found that he hydrogenation of **2** to **3** by complex **F** also is a one-step process. The computed barrier is 106.4 kJ/mol and the reaction is exergonic by 11.8 kJ/mol.

These calculations reveal that **2** is the principal and preferred product. Without external hydrogen supply, the hydrogenation of **1** to **3** as well as **2** to **3** by using complex **F** are not competitive kinetically. This agrees perfectly with the results in Table 2, entries 4-6. Indeed, the dehydrogenation and hydrogenation mechanism is supported by the results obtained in the attempted isomerization of Sobrerol (**1q** in Scheme 4), where only the dehydrogenation product **2q** is found. This two-step mechanism can also explain the isomerization of the homo-allyl alcohol **1l**

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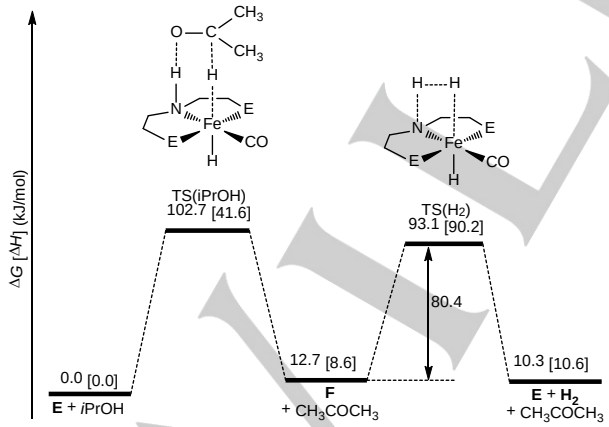
into the corresponding ketone **2l** (Scheme 4), where alcohol dehydrogenation takes place at first, followed by the consecutive C=C bond hydrogenation. The alternative mechanism by which the double bond isomerizes first into the conjugated position was deemed less likely in view of the high barrier for the hydride transfer to the methyl-substituted enone

For testing the stability of the catalysts, we computed the dehydrogenation or hydrogen elimination from complex **F** to complex **E** (**F** = **E** + $H_2$), which has Gibbs free energy barrier of 80.4 kJ/mol, and is slightly exergonic by 2.4 kJ/mol (Scheme 8). Compared with the lower barrier (57.3 kJ/mol) of the facial hydrogenation of **4** to **2a**, complex **F** is stable under the reaction condition. Consequently, once **F** is formed, it will easily hydrogenate **4** to **2** rather than eliminate $H_2$. Since there is no external hydrogen supply, the $H_2$ assisted proton transfer mechanism proposed by Dub and Gordon can be excluded in this work.[21]

For comparison we computed the transfer hydrogenation using isopropanol as external hydrogen source. As shown in Scheme 8, isopropanol dehydrogenation into acetone has Gibbs free energy barrier of 102.7 kJ/mol and is endergonic by 12.7 kJ/mol. This indicates that the dehydrogenation of allyl alcohol is more favored kinetically (92.1 kJ/mol) and thermodynamically (5.0 kJ/mol) and allyl alcohol should be dehydrogenated at first, although isopropanol dehydrogenation is also possible.

Using isopropanol as external hydrogen source [**E** + isopropanol + **1** = **E** + acetone + **3**], the effective barrier of direct hydrogenation of allyl alcohol **1** into alcohol **3** is 126.6 kJ/mol, which is higher than the barrier (92.1 kJ/mol) of allyl alcohol dehydrogenation into the α,β-unsaturated ketone **4** as well as the successive hydrogenation barrier (57.3 kJ/mol) of **4** into **2**a. Therefore, direct allyl alcohol hydrogenation into **3** is kinetically hindered, and the first step should be self-transfer hydrogenation isomerization of allyl alcohol **1** into ketone **2**; and isopropanol in this step plays only the role of solvent.

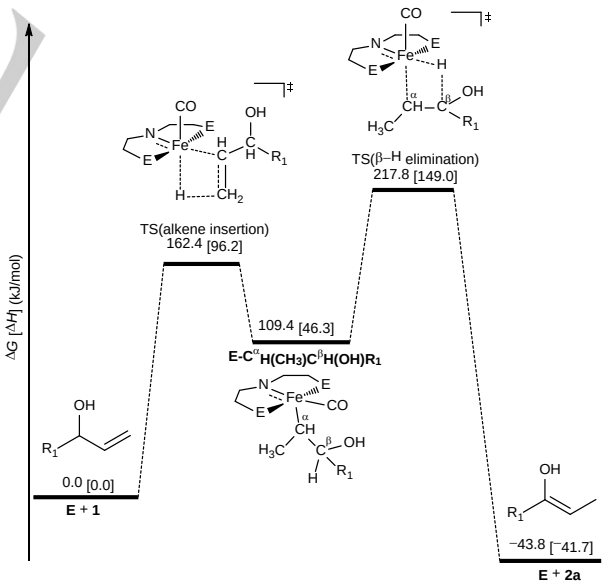



**Scheme 8.** Potential energy surface of *i*PrOH dehydrogenation by **E** as well as $H_2$ elimination from **F** (E = P(*i*Pr)$_2$).

Next we considered the transfer hydrogenation of ketone **2** to alcohol **3** using isopropanol as solvent and hydrogen source [**E** + isopropanol + **2** = **E** + acetone + **3**]. On the basis of the potential energy surfaces (Scheme 7) and isopropanol as hydrogen source (Scheme 8), the effective barrier of the hydrogenation of ketone **2** to alcohol **3** is 119.1 kJ/mol and the total reaction is slightly endergonic by 0.9 kJ/mol. This energetic difference should determine the observed selectivity (Table 2, entry 1). Indeed, the computed ratio between **2** and **3** using isopropanol as hydrogen source [isopropanol + **2** = acetone + **3**] is 10 to 90 (determined by the equilibrium constant and the concentrations of isopropanol and substrate, Supporting information S4), in perfect agreement with the experimentally observed 9 to 90 after 24 hours (Table 1, entry 5). This shows that large excess of isopropanol can shift the reaction towards to the saturated product of **3** under the thermodynamically equilibrated state.

Our computations show that without external hydrogen supply, the reaction of allyl alcohol **1** takes place *via* the self-transfer hydrogenation isomerization mechanism *via* the α,β-unsaturated ketone **4** as intermediate; and the principal product should be the ketone **2**. This is indeed observed for the reaction in benzene or toluene. Using isopropanol as external hydrogen source, the same reaction mechanism can be proposed, however, the formed ketone **2** can be partially hydrogenated into the saturated alcohol on the basis of their thermodynamic properties.

Despite this perfect agreement between theory and experiment, we are also interested to exclude the possibility of an isomerization mechanism via alkene insertion using amido complex **E** (Scheme 9) In this mechanism, the first step should be the insertion of the C=C double bond of the alkene into the Fe-H bond resulting in the formation of the alkyl complex; and the second step should be β-hydride elimination resulting in the formation of isomerized alkene.




**Scheme 9**. Reaction profile for isomerization of **1** to **2** *via* insertion of the alkene mechanism ($R_1$ = $C_5H_{11}$, E = P(*i*Pr)$_2$)

As shown in Scheme 9, the insertion of the Fe-H bond into the C=C double bon of allyl alcohol **1** has Gibbs free energy barrier of 162.4 kJ/mol and the formation of the alkyl intermediate is highly endergonic by 109.4 kJ/mol. The subsequent following β-

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H elimination has Gibbs free energy barrier of 108.4 kJ/mol and the **2** formation is exergonic by 200.1 kJ/mol. The overall isomerization from **1** to **2** has an effective Gibbs free energy barrier of 217.8 kJ/mol, which barrier is much higher than that (92.1 kJ/mol) of allyl alcohol **1** dehydrogenation as well as that (102.7 kJ/mol) of isopropanol dehydrogenation. This indicates that this alkene insertion mechanism is kinetically much hindered and can be discarded accordingly.

## Conclusions

In our study, we have found that in the presence of strong base and without external hydrogen supply, the iron-pincer complex Fe(PNP)(CO)HCl is an excellent catalyst for the isomerization of allylic and homo-allylic alcohols to the corresponding ketones. Both aliphatic and aromatic allylic alcohols are suitable substrates. The aromatic substrates may possess electron-withdrawing or electron-donating substituents, in all possible positions of the phenyl ring. A two-step self-hydrogen-borrowing mechanism *via* a dehydrogenation-hydrogenation isomerization is proposed and was verified by DFT computation. Indeed, this two-step mechanism is also applicable for reactions using alcohol as external hydrogen source, where the isomerized ketones can be further hydrogenated into the corresponding alcohols. The alternative isomerization mechanism via alkene insertion into the iron-hydride bond followed by beta-hydride elimination can be discarded on the basis of the much higher barrier.

## Experimental Section

An oven dried 4 mL pressure tube with a stirring bar was charged with PNPFeXY(CO) (4.5 mg, 0.01 mmol, 1 mol%) and a 0.01 M solution of base in toluene (1.2 mg, 0.01 mmol, 1 mol%) was added sequentially. Then 1 mmol of substrate was added immediately to the pressure tube. The solution was stirred for 1 hour at 80 °C. GC yields were determined with dodecane as internal standard. Isolated yields were obtained by using silica gel chromatography (Cyclohexane: Ethyl Acetate= 50:1) after rotary evaporation. For the neat reaction, base was added together with PNPFeHCl(CO).

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**Keywords:** Isomerization • Ketone •Allylic Alcohol • Iron catalyst • Pincer ligand • DFT

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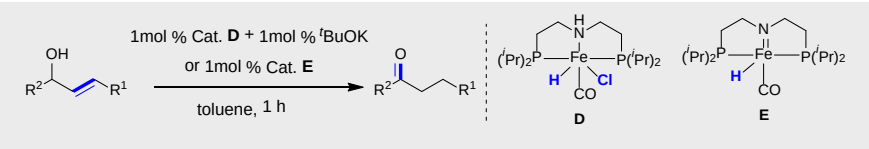


**A borrowing pincer** The isomerization of non-activated allylic alcohols to ketones catalyzed by an iron(II) PNP pincer complex is reported. High reaction rates were achieved, even at room temperature. A self-borrowing hydrogen mechanism was established *via* DFT calculations.

*T. Xia[+], Z. Wei[+], B. Spiegelberg, H. Jiao, S. Hinze, J. G. de Vries**

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**Isomerization of Allylic Alcohols to Ketones with a PNP Pincer Iron Catalyst**

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