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Highly enantioselective isomerization of primary allylic alcohols catalyzed by (P,N)-iridium complexes*

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Abstract: The catalytic asymmetric isomerization of allylic amines to enamines stands out as one of the most accomplished and well-studied reactions in asymmetric catalysis as illustrated by its industrial application. In contrast, the related asymmetric isomerization of primary allylic alcohols to the corresponding aldehydes still constitutes a significant challenge in organic synthesis. Herein, we show that under appropriate reaction conditions, iridium-hydride catalysts promote the isomerization of primary allylic alcohols under very mild reaction conditions. The best catalysts deliver the desired chiral aldehydes with unprecedented levels of enantioselectivity and good yields. Mechanistic hypotheses have been drawn based on preliminary investigations.

Keywords: allylic alcohols; enantioselective catalysis; iridium; isomerization; (P,N) ligands.

INTRODUCTION

The rhodium-catalyzed asymmetric isomerization of allylic amines into the corresponding enamines stands out as one of the major achievements in asymmetric catalysis [1]. The reaction is usually run under mild conditions, and high activities as well as high enantioselectivities have been obtained for a wide range of substrates (eq. 1). The mechanism has been thoroughly studied and is now well understood and accepted [2]. All these aspects taken together have favored the implementation of this isomerization reaction as a key step in the industrial production of menthol [3]. In contrast, the same level of success has not yet been achieved for the corresponding asymmetric isomerization of primary allylic alcohols into aldehydes (eq. 2) [4].
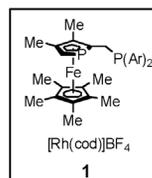
(1)

(2)


Among the very few examples of chiral catalysts reported for this asymmetric transformation, the chiral-planar phosphaferrocene-rhodium complex **1** developed by G. C. Fu and co-workers emerges as the best system reported to date [4e,f]. Nevertheless, this catalyst suffers from several limitations, such as the chiral ligand accessibility, the harsh reaction conditions, and the prolonged reaction times. In addition, the substrate scope appears limited since only a few substrates have been obtained with satisfactory levels of enantioselectivity.

## FROM HYDROGENATION TO ISOMERIZATION OF PRIMARY ALLYLIC ALCOHOLS

In the early 1980s, Crabtree [5] and Stork [6] independently demonstrated that Crabtree's hydrogenation catalyst **2** was directing the hydrogenation of a wide range of allylic and homo-allylic alcohols. This cationic iridium complex was shown to be virtually insensitive to the degree of substitution of the double bond and, hence, to be applicable to a wide array of substrates. Consequently, this elegant and efficient methodology has been applied very often in synthesis since its discovery [7].

We have recently established that one could exclusively isomerize primary allylic alcohols into the corresponding aldehydes without any competing hydrogenation of the double bond by slightly modifying the original experimental protocol [8]. After generating the active dihydride intermediate **3**, the solution mixture is degassed to extrude the excess of molecular hydrogen. The substrate is only added next, and the reaction performed at room temperature to deliver exclusively and quantitatively the desired isomerization product (Fig. 1).
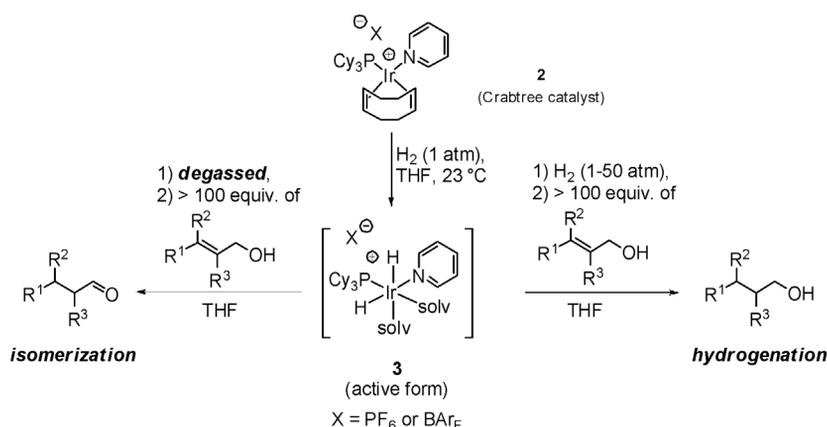
Fig. 1 Hydrogenation vs. isomerization using Crabtree's catalyst.

Similarly to the directed hydrogenation reaction, the scope of the isomerization reaction was found to be relatively broad (Fig. 2). Allylic alcohols with a di-, tri-, or even a tetra-substituted double bond were isomerized quantitatively using low to very low catalyst loadings and short reaction times. More importantly perhaps, in most cases the mild reaction conditions appeared well suited for the development of an enantioselective variant of the process.
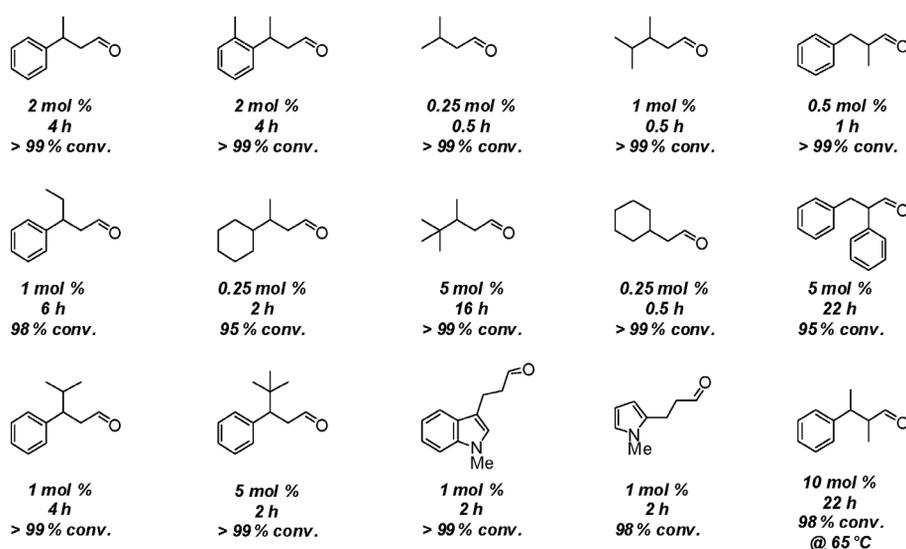
Fig. 2 Substrate scope for the isomerization of primary allylic alcohols using Crabtree's catalyst **2**. All experiments were carried out at room temperature unless otherwise stated.

ASYMMETRIC ISOMERIZATION OF PRIMARY ALLYLIC ALCOHOLS

The obvious next step was to evaluate the potential of known chiral (P,N)-iridium hydrogenation catalysts in the isomerization reaction. (*E*)-4-methyl-3-phenylpent-2-enol was used as a model substrate (eq. 3) in our initial investigations using our experimental protocol that favors isomerization over hydrogenation (*vide supra*). Surprisingly, neither the well-established (phosphinooxazoline)iridium catalyst **4** [9], nor the (quinap)iridium complex **5** recently described by Wang and co-workers [10], nor a Crabtree catalyst analog **6** with a chiral phosphoramidite ligand in place of the tricyclohexylphosphine moiety [11] did provide any isomerization product. When using the (dialkylphosphinite-pyridine)iridium complex **7** [12], less than 20 % of nearly racemic aldehyde was obtained (Fig. 3a).

$$\text{(3)}$$
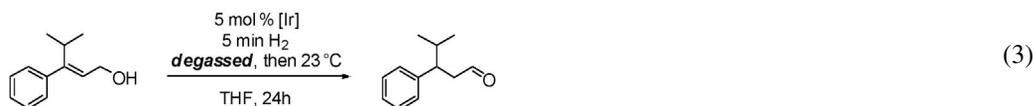
In order to get a better understanding of the electronic and/or steric parameters that may explain the loss of reactivity when going from the achiral catalyst **2** to the chiral catalysts **4–7**, we synthesized a series of Crabtree's catalyst analogs **8–12** (Fig. 3b). Their catalytic performances were evaluated using our model substrate and applying the standard reaction conditions for the isomerization reaction (eq. 3). Any variation of the phosphine moiety led to a complete loss of the catalytic activity. Indeed, no isomerization product was obtained when replacing the strong donor tricyclohexylphosphine by a tri-aryl, a diaryl-alkyl-, or an aryl-dialkyl-phosphine surrogate. Alternatively, using a strong donor NHC carbene ligand instead resulted again in the loss of catalytic activity in the isomerization reaction. A bis-tricyclohexylphosphine iridium complex did not display any catalytic activity either.
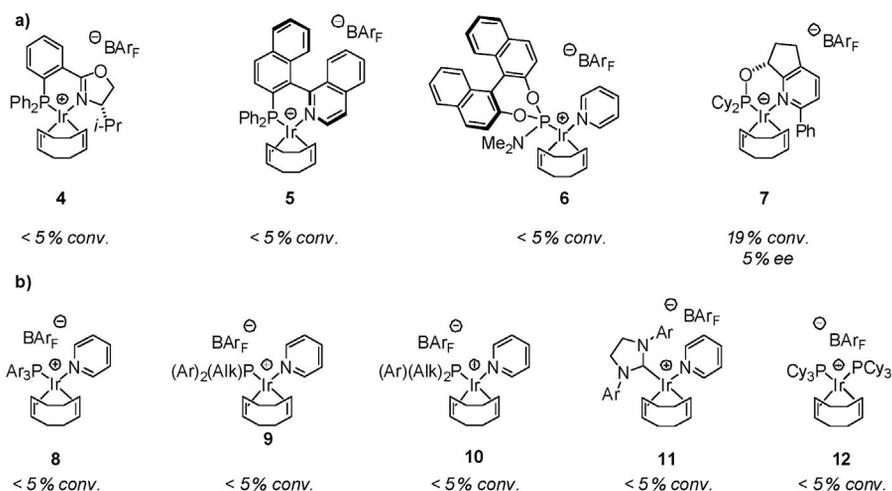
Fig. 3

At this stage of our investigations, we reasoned that a C_1-symmetric (P,N) ligand having a tri-alkyl-phosphine moiety may be crucial to restore the catalytic activity in the isomerization reaction. In this context, the phosphanyl-alkyl-oxazoline scaffold depicted on Fig. 4 appeared particularly attractive. This chiral ligand has been initially developed by Helmchen and co-workers for Pd-catalyzed asymmetric allylic alkylations [13] and later on used in rhodium and iridium asymmetric hydrogenation reactions by the Imamoto and Pfaltz groups, respectively [14,15].
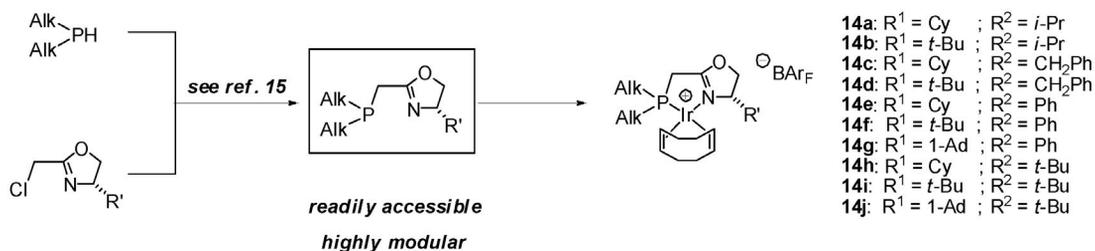

Fig. 4 Synthesis of (phosphanyl-alkyl-oxazoline)iridium complexes.

This structure possesses two of the most important features of a chiral ligand in synthetic methodology: (i) it is accessible in a few steps from the amino acids chiral pool; (ii) it is highly modular since the dialkylphosphine moiety and the oxazoline building block are assembled at a late stage of the synthesis by a high-yielding SN_2 reaction. Furthermore, the iridium complexes derived from this chiral ligand are air-stable and can be purified by standard column chromatography when the very bulky and highly lipophilic BAr_F (tetrakis-[3,5-bis-(trifluoromethyl)phenyl]borate) counter-anion is employed [16].

When we tested the first iridium complex we synthesized (**14a**, Table 1, entry 1) using our test substrate and applying the standard reaction conditions for the isomerization reaction, we were pleased to observe that the catalytic activity in the isomerization reaction was recovered although the enantio-selectivity was only modest.

Table 1
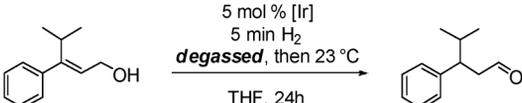
Entry[a]	Catalyst	T (°C)	Time (h)	Conversion (%)[b]	ee (%)[c]
1	(S)-**14a**	23	18	98	11 (R)
2	(S)-**14b**	23	18	75	28 (S)
3	(S)-**14c**	23	2	>99	30 (S)
4	(S)-**14d**	23	2	>99	45 (S)
5	(R)-**14e**	23	2	>99	75 (R)
6	(R)-**14f**	23	2	>99	84 (R)
7	(R)-**14f**	−10	4	>99	90 (R)
8	(R)-**14f**	−30	14	>99	90 (R)
9	(R)-**14g**	23	4	95	91 (R)
10	(R)-**14g**	−10	22	96	93 (R)
11	(S)-**14h**	23	12	>99	89 (S)
12	(S)-**14i**	23	12	98	95 (S)
13	(S)-**14j**	23	22	75	97 (S)

[a]Average of at least two runs.
[b]Determined by GC and/or ^{1}H NMR.
[c]Determined by GC or SFC on a chiral column. Absolute configuration based on the sign of the optical rotation and by comparison with literature data.
[d]The remaining 81 % is a 2:1 mixture of *E/Z*-isomers of the starting material.

The high modularity of the ligand scaffold allowed us to synthesize a small library of 10 different iridium complexes **14a–j**, having in each case a trialkyl phosphine moiety to ensure catalytic activity (Fig 4). A survey of these structures in the asymmetric isomerization reaction indicates that increasing the size of the substituents on the phosphorus atom while keeping the oxazoline substituent constant, systematically improved the enantioselectivity of the product. Derivatives with either a phenyl or a benzyl group displayed faster rates than their alkyl congeners (R = *i*-Pr or *t*-Bu).

The scope of the reaction was investigated next (Table 2). The chiral aldehydes were still obtained with high enantiomeric excesses when the electronic properties of the test substrate were varied by introducing either electron-withdrawing or -donating substituent on the *para*-position of the aromatic ring. The enantioselectivity is improved if the size of the alkyl substituent is increased (from *i*-Pr to Cy or *t*-Bu). A 3,3-dialkyl-allylic alcohol can be isomerized, delivering the corresponding chiral aldehyde in lower yield but with a promising level of enantioselectivity (Table 2, entries 13 and 14). For substrates having smaller alkyl substituents (from *i*-Pr to Me or Et), the best results were obtained with the more reactive catalyst **14g**. Nevertheless, the conversions and enantioselectivites are drastically reduced. The same observation was made when the *Z*-isomer of the test substrate was employed. Interestingly, in these three cases, the remaining starting material is obtained as a mixture of *E/Z* configured allylic alcohols.

Table 2

$$\text{R}^2\underset{\text{OH}}{\overset{\text{R}^1}{\diagup\diagdown}} \xrightarrow[\text{THF, 0.05 M}]{\begin{array}{c}\text{5 mol \% [Ir]}\\\text{5 min H}_2\\ degassed,\ \text{then 23 °C}\end{array}} \text{R}^2\overset{\text{R}^1}{\diagup\diagdown}\text{O}$$

Entry[a]	Catalyst	R^1	R^2	Time [h]	Conversion (%)[b]	ee (%)[c]
1	(R)-**14g**	i-Pr	4-Me-C$_6$H$_4$	22	84	86 (R)
2	(S)-**14j**	i-Pr	4-Me-C$_6$H$_4$	22	71	95 (S)
3	(R)-**14g**	i-Pr	4-MeO-C$_6$H$_4$	22	>99	90 (R)
4	(S)-**14j**	i-Pr	4-MeO-C$_6$H$_4$	22	91	94 (S)
5	(R)-**14g**	i-Pr	4-Cl-C$_6$H$_4$	22	88	82 (R)
6	(S)-**14j**	i-Pr	4-Cl-C$_6$H$_4$	22	60	94 (S)
7	(R)-**14g**	Me	C$_6$H$_5$	22	10[d]	57 (S)
8	(R)-**14g**	Et	C$_6$H$_5$	22	30[d]	73 (S)
9	(R)-**14g**	Cy	C$_6$H$_5$	6	85	94 (R)
10	(S)-**14j**	Cy	C$_6$H$_5$	22	88	98 (S)
11	(R)-**14g**	t-Bu	C$_6$H$_5$	22	80	99 (R)
12	(S)-**14j**	t-Bu	C$_6$H$_5$	22	81	>99 (S)
13	(R)-**14g**	Me	Cy	22	90	68 (S)
14	(S)-**14j**	Me	Cy	18	25	76 (R)
15	(R)-**14g**	Ph	i-Pr	22	26[e]	46 (S)
16	(R)-**14g**	Ph	Me	22	18	25 (R)

[a]Average of at least two runs.
[b]Determined by GC and/or ^{1}H NMR.
[c]Determined by GC or SFC on a chiral column. Absolute configuration based on the sign of the optical rotation and by comparison with literature data.
[d]A mixture of E/Z-isomers was recovered.
[e]The remaining 74 % is a 3.5:1 mixture of E/Z-isomers.

In order to obtain preliminary insights into the mechanism for the isomerization reaction, a series of complementary experiments was performed. X-ray crystallographic analysis of catalyst **14g** [17] shows that three of the four quadrants are spatially occupied; two by the bulky adamantyl substituents at the phosphorus atom and one by the phenyl ring at the stereogenic center of the oxazoline (Fig. 5a). Activation of the same iridium complex by molecular hydrogen followed by degassing of the THF-d_8 solution shows the formation of a major cis-dihydride intermediate ($^2J_{HP}$ = 20 Hz) reminiscent of the active form of Crabtree's catalyst. The position of the apical hydride could not be ascertained by two-dimensional NMR spectroscopy. Nevertheless, this indicates that the north- and south-western quadrants are "electronically" occupied and suggests that the substrate may preferentially bind on the remaining open quadrants (Fig. 5b).

Labeling experiments were performed using a 1,1-dideuterated analog of our test substrate. Observation of the monodeuterated product along with the dideuterated aldehyde supports an inter-molecular process in which both hydrides are transferred from the catalyst to the substrate since the extent of H incorporation turned out to be twice proportional to the initial catalyst loading (Fig. 5c).
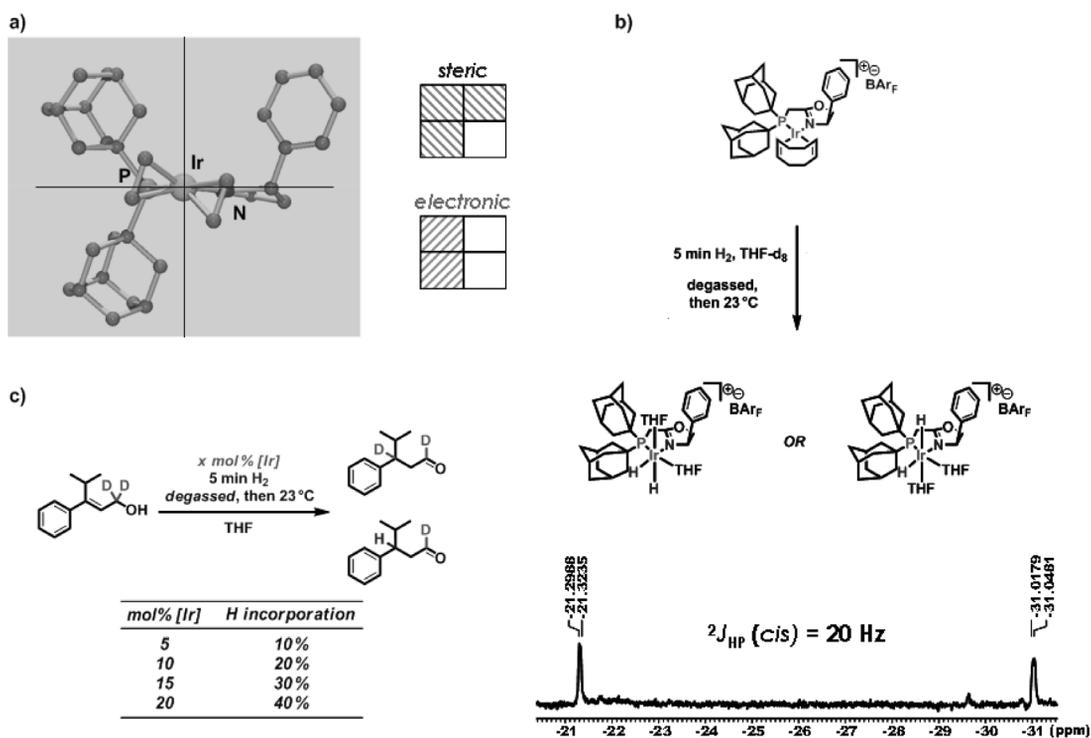
Fig 5 (a) X-ray structure of catalyst **14g**. The anion and the methylene carbons of the cyclooctadiene moiety have been omitted for clarity [Ir-N = 2.110(6) Å; Ir-P = 2.345(5) Å; N-Ir-P = 82.43(17)°]; (b) Monitoring of the activation of precatalyst **14g** by NMR spectroscopy. The hydride region is shown; (c) Labeling experiment using catalyst **14g**.

Based on our observations, the catalytic cycle depicted on Fig. 6 is proposed to be operating for the asymmetric isomerization of primary allylic alcohols catalyzed by iridium complexes **14**. Activation of the precatalyst in tetrahydrofuran (THF) leads to the dihydride intermediate observed by ^{1}H and ^{31}P NMR spectroscopy, the structure of which is reminiscent of the active form of Crabtree's hydrogenation catalyst. Supported by the studies on the directed hydrogenation of allylic alcohols, displacement of the two solvent molecules and two-point binding of the substrate is expected. The conformational binding of the substrate is believed to be crucial in the isomerization reaction since this is at the stage of the catalytic cycle that all the stereochemical elements are installed. If migratory insertion takes place at C(2), a secondary alkyl-iridium-hydride intermediate is generated (Fig. 6, left-hand side of the catalytic cycle). Subsequent, decoordination of the alcohol functionality and β-hydride elimination delivers an enol-iridium-dihydride species. Upon release, the liberated chiral enol tautomerizes—presumably outside the catalytic cycle [18]—and concomitantly the active *cis*-dihydride intermediate is regenerated. If migratory insertion takes place at C(3), a tertiary alkyl-iridium-hydride intermediate is generated (Fig. 6, right-hand side of the catalytic cycle). At this stage, reductive elimination would lead to the saturated alcohol formally resulting from hydrogenation. In the absence of extra hydrogen and/or hydrogen pressure, this pathway is probably too high in energy since we never observed any traces of the hydrogenation product by either GC or NMR spectroscopy. Instead, decoordination of the alcohol and β-hydride elimination of the diastereotopic proton at C(2) leads to an intermediate where the coordinated allylic alcohol now has a *Z* configuration.
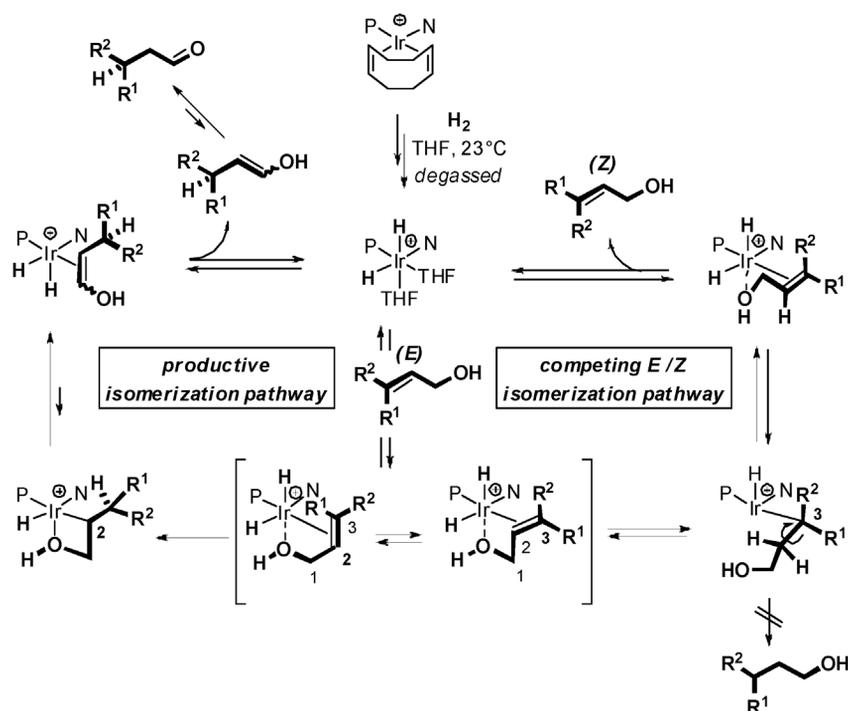
Fig. 6 Proposed catalytic cycle.

In conclusion, we have identified highly active and selective iridium catalysts for the asymmetric isomerization of primary allylic alcohols. We have demonstrated that by adequately tuning the experimental protocol, hydrogenation could be avoided and isomerization exclusively promoted. The nature of the donor atoms in the ligand is crucial. C_1-symmetric (P,N) ligands having a trialkylphosphine moiety were found to be unique at promoting this challenging transformation under unprecedented mild reaction conditions. Preliminary investigations have helped identify and understand essential features of the reaction mechanism.

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17. CCDC-724940. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <www.ccdc.cam.ac.uk/data_request/cif>.
18. The tautomerization is presumably taking place outside the catalytic cycle, since attempts to isomerize 2,3-disubstituted allylic alcohols gave the corresponding α-substituted aldehydes in racemic form. The tautomerization is the enantio-determining step for 2,3-disubstituted allylic alcohols. If the metal is not involved or if background tautomerization is too fast, racemic product is expected. For a relevant discussion, see: S. Bergens, B. Bosnich. *J. Am. Chem. Soc*. **113**, 958 (1991).