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Highlight Review

Platinum Metals in the Catalytic Asymmetric Isomerization of Allylic Alcohols

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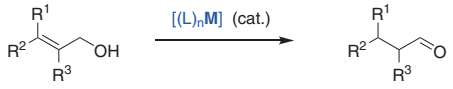
Abstract

Past and recent advances in the metal-catalyzed asymmetric isomerization of allylic alcohols into carbonyl compounds are discussed in the present *Highlight*. Emphasis is placed on rhodium, ruthenium, and iridium; the only three metals that have proven successful to date for this most challenging transformation.

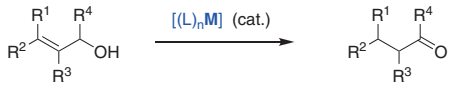
♦ Introduction

The metal-catalyzed asymmetric isomerization of primary and secondary allylic alcohols into the corresponding aldehydes and ketones—a reaction of both academic and industrial relevance—has attracted renewed interest in recent years.[1] Because such transformations undergo refunctionalization upon isomerization, they are often described as internal redox processes and from a synthetic viewpoint, legitimately placed at the very top of the atom-economy scale (Scheme 1).[2] Although a variety of transition metals displays interesting catalytic activity for the non-asymmetric isomerization of some allylic alcohols with TOF up to 62500,[3] the substrate generality remains a major limitation. In most cases, the catalytic activity tends to decrease as a function of the degree of substitution of the olefinic double bond and thus limits investigation of substrates with a prochiral double bond. Catalysts that are effective for the isomerization of primary allylic alcohols are less active for secondary allylic alcohols as is the converse. Furthermore, the lack of supporting organometallic chemistry and the limited number of thorough mechanistic studies using achiral catalysts constitute severe bottlenecks in the rationalized development of highly active and selective chiral catalysts for the related asymmetric isomerization reactions.

Asymmetric isomerization of primary allylic alcohols into aldehydes



Asymmetric isomerization of secondary allylic alcohols into ketones



Scheme 1. Isomerization of primary and secondary allylic alcohols into aldehydes (top) and ketones (bottom) respectively.

The focus of the present *Highlight* is placed exclusively on chiral catalysts elaborated around rhodium, iridium, and ruthenium, three of the Platinum Metals which have been applied with various success to the asymmetric isomerization of primary and secondary allylic alcohols.

♦ Primary Allylic Alcohols

The asymmetric isomerization of primary allylic alcohols into chiral aldehydes is historically intimately linked to the related isomerization of allylic amines into chiral enamines.[4–6] The degree of refinement attained by this rhodium-catalyzed process in terms of activity, selectivity, generality, and practicality is exceptional and has helped defining standards of excellence; very few other catalytic asymmetric transformations have reached to date. In contrast, the asymmetric isomerization of allylic alcohols does not belong to this elite category. Because of the apparent similarity between both isomerization reactions, and the influence of the success story of the cationic [(binap)Rh] system for the isomerization of allylic amines, most of the subsequent catalysts have been designed using chiral bidentate phosphines and rhodium for the isomerization of primary allylic alcohols. The initial studies conducted in the early 80s' showed that [(binap)Rh(cod)]ClO_4 **1** (cod: 1,5-cyclooctadiene) was also catalytically competent for the isomerization of primary allylic alcohols in refluxing THF.[6b,6c] Nevertheless, benchmark substrates such as geraniol and (*E*)-3-phenylbut-2-enol were isomerized with moderate chemical yield and low enantiomeric excess (70% yield, 37% ee and 47% yield, 53% ee respectively) when compared to their allylic amine analogs (Figure 1).

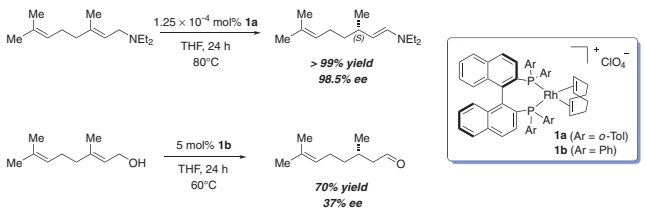


Figure 1. Comparative results for the asymmetric isomerization of (diethyl)geranylamine and geraniol catalyzed by rhodium complex **1**.

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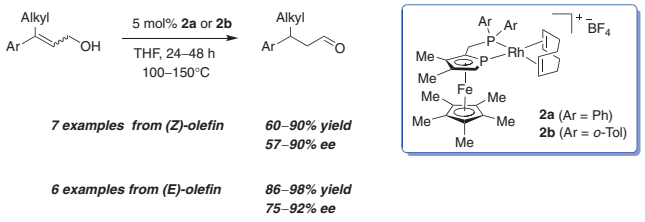

Figure 2. Asymmetric isomerization of allylic alcohols using chiral planar bisphosphine–rhodium catalyst **2**.

At the turn of the century, researchers at Firmenich SA, systematically investigated the potential of a series of privileged chiral ligands in combination with $[Rh(cod)_2]CF_3SO_3$ to perform the asymmetric isomerization of geometrically pure geraniol and nerol.[7,8] The best results were obtained with axially chiral bisphosphine ligands and citronellal was obtained in good yields with ee up to 61% from geraniol and 51% from nerol. Alcohols with (*E*)- and (*Z*)-geometry led to aldehydes with opposite absolute configurations in all cases. At the same period of time, the Fu group reported the synthesis and successful application of two generations of chiral planar phosphaferrocene ligands for the rhodium-catalyzed enantioselective isomerization of aromatic allylic alcohols.[9] While catalyst **2a** showed unprecedented selectivity for (*Z*)-configured substrates, catalyst **2b** displayed a wider applicability and proved efficient both for (*E*) and (*Z*) double bond geometry. Crossover and labeling experiments were instrumental in identifying an intramolecular 1,3-migration pathway when using these rhodium catalysts. The low reactivity, the limited accessibility of the chiral ligand, and the relatively narrow substrate scope have presumably restricted the application of this catalyst in the synthesis of more complex molecules (Figure 2). Applying strictly the same reaction conditions, a similar study was conducted using only three of the many commercially available phosphoramidite ligands.[10] No improvement in activity, selectivity, or scope was thus achieved (5 examples, 84–89% yield, 38–70% ee).[11]

Building on the observation that Crabtree's hydrogenation catalyst $[(Cy_3P)(C_6H_5N)Ir(cod)](PF_6)$ **3** may perform unexpected isomerization for certain olefinic substrates,[12] Mazet and co-workers have recently developed a protocol which enables the exclusive isomerization of a variety of primary allylic alcohols into aldehydes under very mild reaction conditions.[13] Molecular hydrogen was used to generate the active form of the catalyst but was extruded from the reaction media prior to addition of the allylic alcohols to prevent competing hydrogenation. Interestingly, the use of the weakly coordinating BAr_F anion (BAr_F: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) provided enhanced stability of the precatalyst along with improved catalytic performance.[14] The simple modification of the experimental protocol allowed to expand significantly the scope offered by this transition metal which was limited almost exclusively to substrate with a terminal olefin.[1] With catalyst **3** and the reaction conditions developed by the Mazet group even primary allylic alcohols with a tetrasubstituted double bond were isomerized quantitatively. The combination of a (trialkyl)phosphine ligand with a N-donor atom was found to be essential to observe any catalytic activity (Figure 3; top). This favored the subsequent development of three distinct generations of iridium catalysts supported by highly modular chiral (dialkyl)phosphinoalkyloxazoline ligands for the asymmetric isomerization of a variety of (*E*)-configured 3,3-disubstituted primary allylic alcohols. High activity and excellent levels of enantioselectivity were obtained with the first generation of catalyst **4** for the most sterically biased primary allylic alcohols.[15,16] Compelling mechanistic evidences were gathered and support an unprecedented dihydride mechanism which prefers the favored β-H elimination (isomerization pathway) over classical reductive elimination (hydrogenation pathway).[17] The competing (*E*)/(*Z*) isomerization pathway observed for the sterically less demanding and the (*Z*)-configured substrates is also consistent with the proposed mechanism. Following an approach established by Burgess and co-workers,[18] the chiral ligands of second generation were synthesized using abundant and inexpensive L-serine as an alternative to the non-natural and expensive *tert*-leucine used in the synthesis of catalysts such as **5**. The best catalyst displayed similar results for the aromatic primary allylic alcohols (40–99% yield, 94–99% ee) and imparted higher levels of enantioselectivity for the notoriously more challenging purely alkyl-substituted allylic alcohols (20–79% yield, 53–90% ee) (Figure 3; bottom).[19]

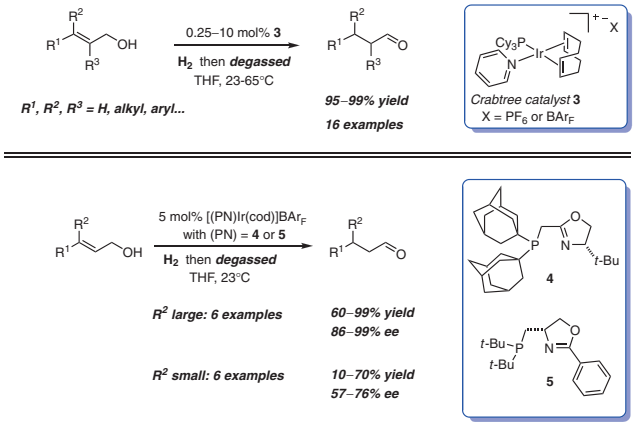

Figure 3. Top: isomerization of allylic alcohols using Crabtree catalyst **3**. Bottom: iridium-catalyzed asymmetric isomerization of 3,3-disubstituted allylic alcohols with chiral PN ligands **4** and **5**.

The strong influence of steric factors on the enantioselectivity was established on the basis of a linear free energy relationship between the ee values and the size of the smallest substituents of the substrate.[20] It served to design a third generation of chiral (dialkyl)phosphinoalkyloxazoline ligands.[21] A simple homologation of the bridge linking the P and N units together enabled an increase of the steric bulk at the proximity of the reactive sites while maintaining enough flexibility to ensure two point-binding of the allylic alcohols. Higher enantioselectivities were indeed obtained for substrates with small alkyl groups thus validating the modification of the ligand scaffold although the yields of the enantioenriched aldehydes remained moderate to low in most cases (Figure 4).

With this last generation of iridium catalyst, geraniol was isomerized into citronellal in 49% yield and 82% ee, a value which coincidentally matches the enantiopurity of the natural product (Figure 5). Noticeably, (*Z*)-configured and tetrasubstituted primary allylic alcohols remained also unchallenged by this latest generation of iridium catalyst.

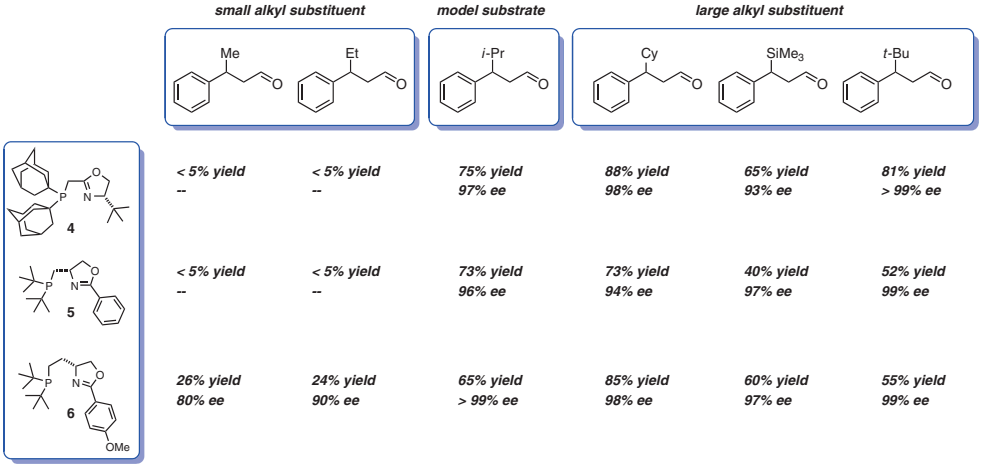

Figure 4. Comparison of the three generations of (P,N) ligands for the asymmetric isomerization of aromatic primary allylic alcohols.

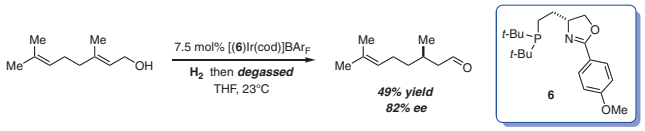

Figure 5. Asymmetric isomerization of geraniol using **6**.

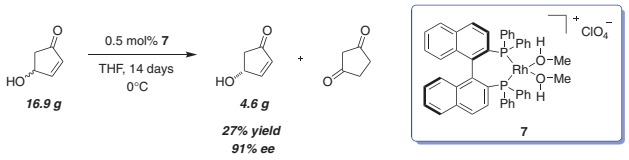

Figure 6. Kinetic resolution of 4-hydroxycyclopent-2-enone with rhodium catalyst **7**.

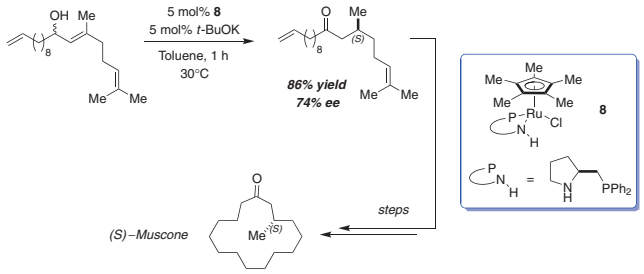

Figure 7. Asymmetric isomerization of secondary allylic alcohols using catalyst **8** and synthesis of (*S*)-muscone.

♦ Secondary Allylic Alcohols

A survey of the literature reveals that the number of efficient chiral catalysts for the asymmetric isomerization of secondary allylic alcohols is rather limited.

Chiral rhodium catalysts were used to perform the kinetic resolution of 4-hydroxycyclopent-2-enone, a key precursor in the asymmetric synthesis of prostaglandins (Figure 6).[23]

The (*R*)-enantiomer of the enantioenriched starting material was obtained in 91% ee and 27% yield (selectivity factor $S = 5$) using only 0.5 mol % of **7**. The same catalyst was later used for the desymmetrization of tricyclic *meso*-1,4-enediol ethers.[24] Unfortunately, the resulting hydroxy ketones were isolated only with modest enantioselectivity. Interestingly, much higher enantioselectivity values were obtained with the corresponding silylated analogs (up to 98% ee).

The privileged binap ligand was also associated with *cis*-$[Ru(MeCN)_2(COD)(\eta^3\text{-}C_3H_5)](BF_4)$ for the kinetic resolution of geometrically pure (*Z*)-2-buten-2-ol, albeit with moderate success. A maximum ee value of 42% at 50% conversion was measured.[25] Half-sandwich bifunctional [Cp*Ru(PN)] catalysts developed in the Ikariya group for the hydrogen transfer between alcohols and ketones were found to be competent in the isomerization of various secondary allylic alcohols. When a chiral PN ligand derived from L-proline was employed, the dynamic kinetic resolution of racemic (*E*)- and (*Z*)-4,8-dimethylnona-3,7-dien-2-ol furnished quantitatively the corresponding chiral ketones in 66% ee and 62% ee respectively. This method was applied to the expedient asymmetric synthesis of both antipodes of muscone. The (*R*)-enantiomer was obtained in 64% ee from a (*Z*)-allylic alcohol whereas the (*S*)-enantiomer was isolated in 74% ee from the (*E*)-configured substrate (Figure 7).[26]

Nine distinct $[(\eta^6\text{-arene})RuCl_2(P)]$ complexes, where P is a chiral monodentate phosphoramidite ligand, have been recently reported by Crochet, Gimeno, and co-workers. These air-stable solids were used in the kinetic resolution of a variety of aryl-2-propenol derivatives. Although the selectivity factors obtained were not in a useful range ($S = 1.6$), the high modularity of the phosphoramidite ligands and the piano-stool ruthenium complexes bodes well for the development of improved generation of catalysts analogous to **9** (Figure 8).[27]

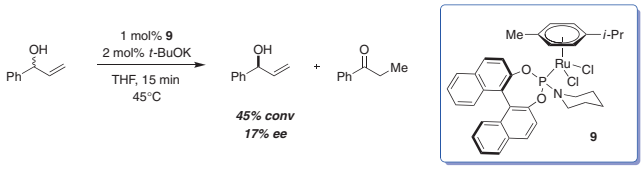

Figure 8. Kinetic resolution of phenylprop-2-enol with ruthenium catalyst **9**.

♦ Conclusion and Outlook

The asymmetric isomerization of allylic alcohols is still far from having reached the level of refinement of the corresponding isomerization of allylic amines. Nevertheless, the recent advances, in particular in iridium catalysis, seem to offer new horizons for primary allylic alcohols. Among them, the stereocontrolled isomerization of substrates with a 2,3-substitution pattern[28] or a tetrasubstituted double bond would enable generation of α-chiral aldehydes or aldehydes with two contiguous stereogenic centers, respectively. From a synthetic standpoint, the isomerization of secondary allylic alcohols holds as much potential. The recent results by Ikariya, Crochet, and Gimeno offer optimistic perspectives in particular with respect to the high synthetic modularity of the ruthenium catalysts.

It is also striking to observe that to date, only rhodium, ruthenium and more recently iridium-based chiral catalysts have been effective for the asymmetric isomerization of allylic alcohols. It would be interesting to explore not only the potential of their related congeners in the platinum series (M = Os, Pd, and Pt) but also to investigate the ability of more abundant, less expensive, and environmentally friendly first-row transition metals for this transformation.

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