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Recent Progress in Iridium-Catalyzed Enantioselective Hydrogenation: Tetrasubstituted Olefins and Polyenes

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Abstract: Iridium-catalyzed enantioselective hydrogenation has become the method of choice to convert prochiral unfunctionalized olefins to optically active compounds. Recently, we reported on applications giving access to more than one stereocenter in a single hydrogenation step. In this account we present recent developments in the hydrogenation of tetrasubstituted unfunctionalized olefins and isoprenoid polyenes, which allow the generation of two stereocenters in a single hydrogenation step.

Keywords: Asymmetric catalysis · Hydrogenation · Iridium · N,P Ligands · Tetrasubstituted olefins

The development of chiral rhodium-diphosphine hydrogenation catalysts 40 years ago[1] marked the beginning of the modern era of asymmetric catalysis. Today asymmetric hydrogenation is one of the most powerful catalytic methods for the preparation of optically active compounds.[2] High enantioselectivity, low catalyst loadings, essentially quantitative yields, perfect atom economy, and mild conditions are attractive features of this transformation. So it is not surprising that since the early 1970s, when the well-known L-Dopa process was established at Monsanto,[3] hydrogenation is playing a dominant role in industrial asymmetric catalysis.

When we started our work on chiral iridium-PHOX complexes (PHOX = phosphinooxazoline; structure **Ir-1**, Fig. 1) more than 10 years ago, we anticipated that these complexes would open up new possibilities in asymmetric hydrogenation. At that time, the range of olefins that could be reduced with high enantioselectivity was limited to certain classes of properly functionalized alkenes. Although many efficient, highly enantioselective rhodium- and ruthenium-diphosphine catalysts were known, they all required a coordinating group next to the C=C bond. In the absence of a suitable coordinating substituent these catalysts showed insufficient reactivity and the enantioselectivities were generally low. In analogy with the Crabtree catalyst,[5] which also has a cationic Ir(I) center bound to a nitrogen and a phosphorus atom, we expected Ir-PHOX complexes to be sufficiently reactive to allow hydrogenation of tri- and even tetrasubstituted unfunctionalized olefins. We thought, provided that the chiral P,N-ligands induced practically useful levels of enantioselectivities, such catalysts would considerably expand the scope of asymmetric hydrogenation. Because they would not require the presence of any specific substituent next to the C=C bond, they could be applied to a wide range of olefins.

Initial experiments with aryl-substituted unfunctionalized olefins confirmed our expectation that Ir-PHOX complexes were

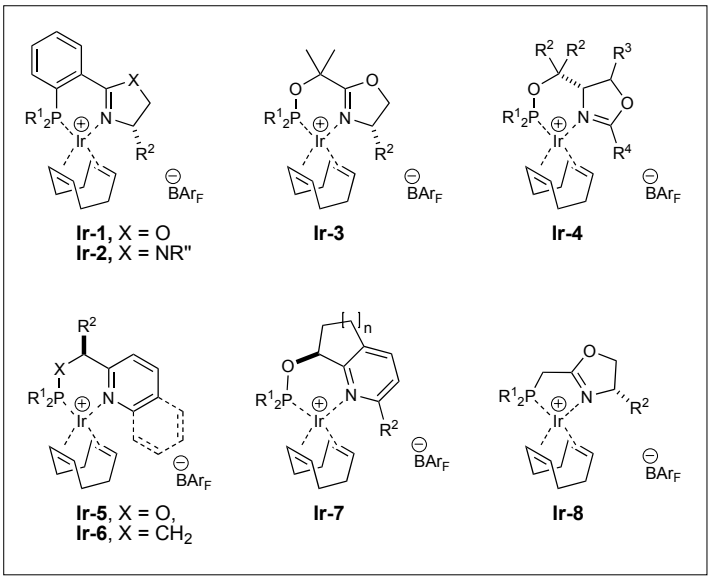

Fig. 1. Iridium catalysts for enantioselective hydrogenation of unfunctionalized olefins[4]

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highly reactive hydrogenation catalysts.[6] Much to our delight, they also gave very promising enantioselectivities. However, catalyst deactivation during the reaction led to incomplete conversions when using low catalyst loadings. Fortunately, after a long period of fruitless experiments, Andrew Lightfoot in our lab finally found a surprisingly simple solution to avoid catalyst deactivation: replacement of the hexafluorophosphate counterion with BAr_F (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) had a dramatic effect on the catalyst stability and allowed catalyst loadings to be reduced below 0.1 mol%.[7] Under optimized conditions, full conversions with turnover numbers of >5000 could be achieved. Importantly, the complexes with the BAr_F counterion proved to be oxygen and moisture tolerant, allowing the reactions to be set up in the air without special precautions.

Having solved the deactivation problem, we focused our research on the search for new P,N-ligands in order to enhance the scope of our iridium catalysts. The most versatile ligand complexes, which gave excellent results for a wide range of unfunctionalized as well as certain functionalized olefins, are shown in Fig. 1. Over the last few years several other research groups have also contributed to the development of new chiral iridium catalysts.[8] Most notable are the oxazole- and thiazole-based P,N-ligands reported by Andersson and coworkers[9] and the C,N-ligands with a coordinating N-heterocyclic carbene unit developed by the Burgess group.[10]

To date, a wide range of unfunctionalized olefins can be hydrogenated enantioselectively in order to establish a single stereocenter with high enantiocontrol.[11] We envisaged that iridium-catalyzed enantioselective hydrogenation could also be used to establish more than one stereocenter in a single step by hydrogenation of a tetrasubstituted olefin or a di- or polyene. Here we discuss our recent results in this area which demonstrate the potential of chiral iridium catalysts for the stereoselective synthesis of complex molecules

Tetrasubstituted Olefins[12]

Among the olefins tested in our group and other labs, unfunctionalized tetrasubstituted olefins have proved difficult to hydrogenate due to low catalyst activity and/or poor enantioselectivity. Although the tetrasubstituted olefin **11** is not suitable for generating two stereocenters, it helped us to understand the reactivity of tetrasubstituted olefins in comparison with structurally similar trisubstituted olefins **9** and **10** (Fig. 2). While olefins **9** and **10** can be hydrogenated with very high enantioselectivity (**9**: >99% *ee*, **10**: 98% *ee*[4e]) only a few catalysts gave full conversion for olefin **11** and only moderate enantiomeric excesses of up to 81% were obtained.

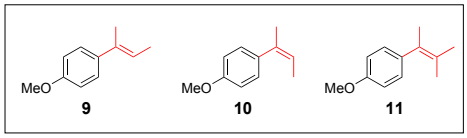


Fig. 2

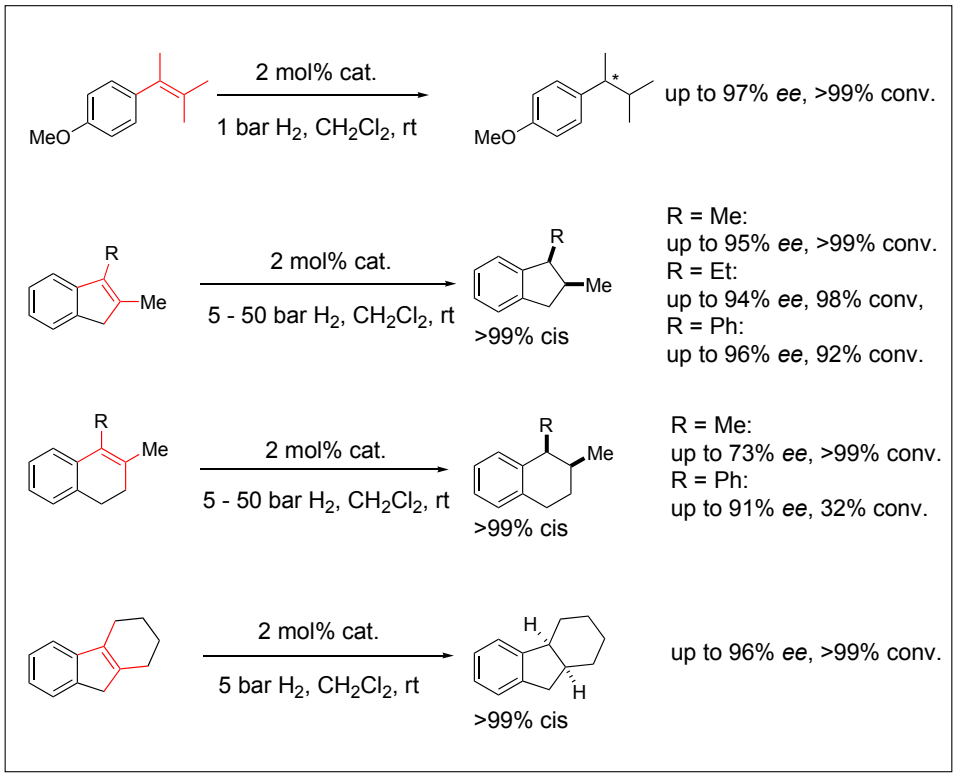
We envisaged that sterically less demanding ligands would facilitate coordination of the olefin to the metal. Therefore, we used a ligand structure in the synthesis of new iridium catalysts which had previously been used by Helmchen in allylic alkylation reactions.[13] These ligands form a five-membered chelate ring (**Ir-8**) and therefore open the coordination sphere around the iridium center. While the enantiomeric excesses obtained with most new catalysts in the hydrogenation of trisubstituted olefins were comparable or worse than those obtained with other catalysts, all new complexes showed high activity in the hydrogenation of olefin **11** with some giving greater than 90% *ee*. Various other tetrasubstituted olefins also reacted with high rates and good to excellent enantioselectivity. Lowering the H_2-pressure had a very positive effect, when complexes of type **Ir-8** were used. During initial studies on **11** an *ee* of 92% was obtained at 50 bar, but when we lowered the pressure to 1 bar, olefin **11** was hydrogenated within 3 h with 97% *ee*. This demonstrates the user-friendly nature of our catalyst system. Tricyclic olefins which can serve as valuable precursors for a variety of natural products can also be reduced with high enantioselectivity at remarkably low catalyst loading (0.1 mol%). Our recent results in the enantioselective hydrogenation of unfunctionalized tetrasubstituted olefins are summarized in Scheme 1. The high catalytic activity of iridium catalysts towards tetrasubstituted olefins provides the option to introduce two adjacent stereogenic centers in a single step, opening new possibilities for asymmetric hydrogenation.

Enantio- and Diastereoselective Hydrogenation of Polyenes

Both conjugated and non-conjugated polyenes are possible substrates. Burgess and coworkers recently published the diastereoselective hydrogenation of a chiral diene to access α,ω-functionalized 2,4,6-trimethylheptane triads thus establishing two stereocenters in a single step (Scheme 2).[14]

In our work we focused on the hydrogenation of non-conjugated isoprenoid polyenes, which can serve as valuable precursors for terpenoid natural products, such as vitamins E and K[15] or related antioxidants[16] and pheromones.[17] A key for the success of this project was our recent discovery of a class of iridium-catalysts (**Ir-7**)[4e] which enabled us to reduce unfunctionalized, purely alkyl-substituted olefins.[18]

Using this class of iridium-catalysts for the hydrogenation of α- or γ-tocotrienyl ac-



Scheme 1. Enantioselective hydrogenation of tetrasubstituted unfunctionalized olefins[12]

etate provided almost exclusively the natural (*RRR*)-isomer of α- or γ-tocopheryl acetate, thus providing a highly effective stereoselective route to this important class of bioactive antioxidants (Scheme 3).[18]

The success of our methodology stimulated us to further investigate the scope of this strategy. In our earlier studies we had already shown that *cis*- and *trans*-olefins **9** and **10** are converted to products of opposite configuration.[6] Therefore, the sense of asymmetric induction can be controlled by proper choice of the double bond geometry. We now applied this concept in the enantio- and diastereoselective hydrogenation of farnesol.

We envisaged that by proper choice of the double bond geometry it should be possible to prepare each of the four stereoisomers of hexahydrofarnesol stereoselectively. Indeed, all four stereoisomers of farnesol were formed with high enantio- and diastereoselectivity using the same catalyst **Ir-12** (Scheme 4).[19]

Alternatively, a stepwise approach starting from only one geometrical isomer may be taken. Since unfunctionalized C=C bonds do not react with Ru-diphosphine catalysts, the C=C bond of the allylic alcohol moiety of farnesol can be reduced selectively without affecting the trialkyl substituted C=C bonds. Subsequent hydrogenation of the remaining two C=C bonds with a suitable iridium-catalyst then gives the desired hexahydrofarnesol with high stereoselectivity (Scheme 5).[19] Because the Ru and Ir catalysts are available in both enantiomeric forms, each of the four stereoisomers can be obtained from (*E,E*)-farnesol using the proper combination of (*R*) or (*S*) catalysts.

Conclusion

The hydrogenation of tetrasubstituted olefins and polyenes provides an attractive and direct route to chiral products with two or more stereogenic centers. By using the appropriate combination of catalyst configuration and double bond geometry, each of the possible stereoisomeric products can be readily prepared with the desired absolute and relative configuration at the new stereocenters. This strategy offers many opportunities for the synthesis of complex chiral molecules.

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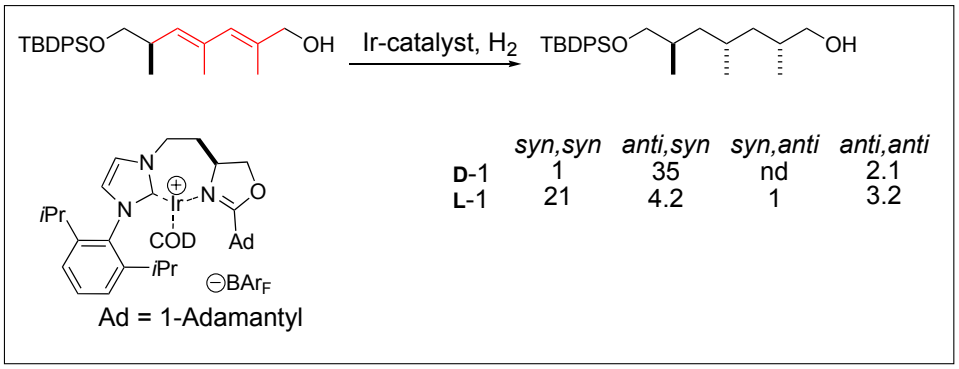
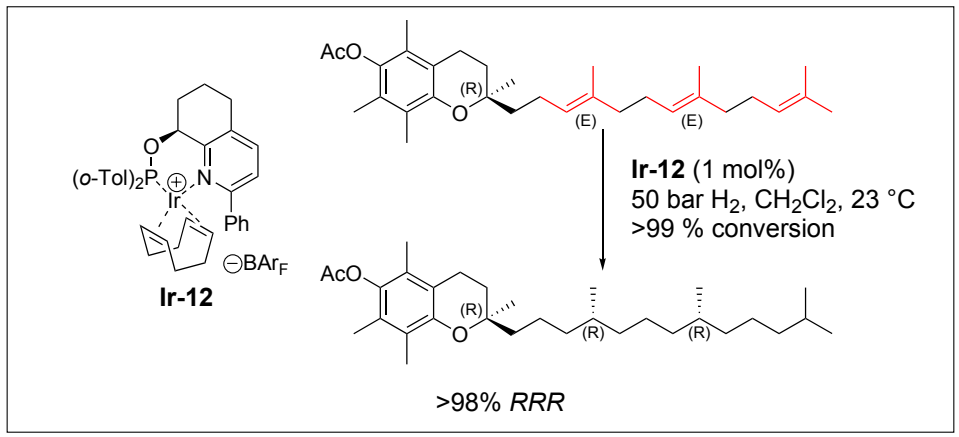
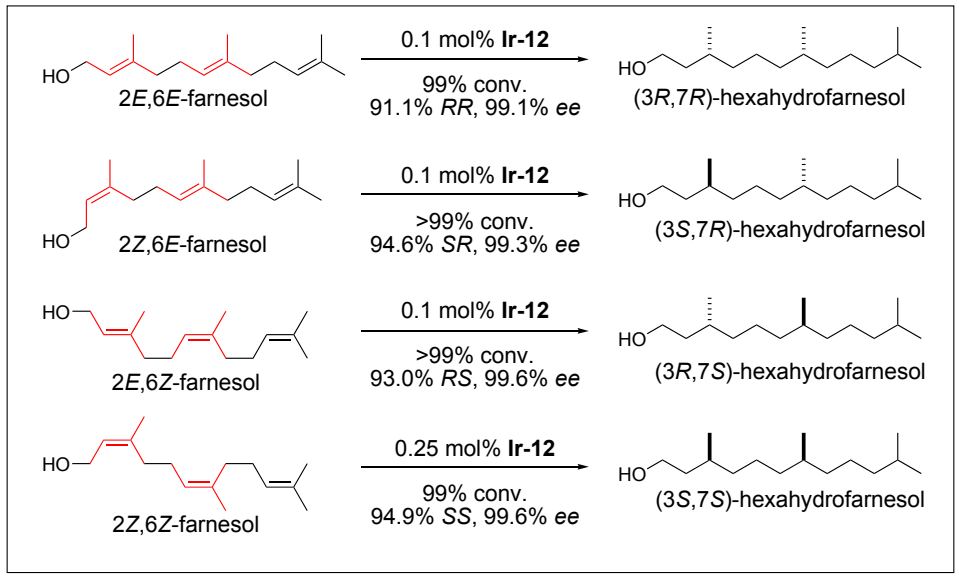


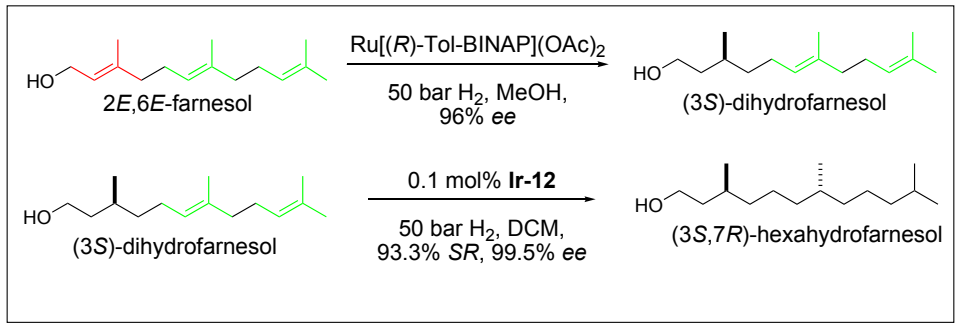
Scheme 2. Stereoselective hydrogenation of a diene[14]



Scheme 3. Stereoselective hydrogenation of γ-tocotrienyl acetate[18]



Scheme 4. Iridium-catalyzed hydrogenation of farnesol stereoisomers[19]



Scheme 5. Consecutive Ru- and Ir-catalyzed hydrogenation of (2*E*,6*E*)-farnesol[19]

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