Asymmetric Hydrogenation

DOI: 10.1002/anie.201302942

Remotely Controlled Iridium-Catalyzed Asymmetric Hydrogenation of Terminal 1,1-Diaryl Alkenes**

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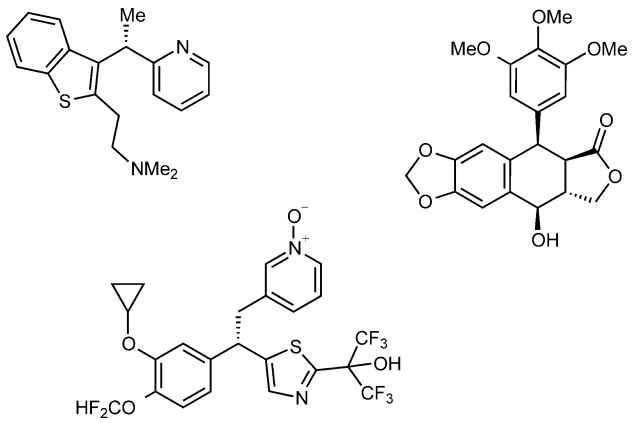
asymmetric hydrogenation · directing groups · enantioselectivity · iridium catalysts · terminal alkenes

The transition-metal-catalyzed asymmetric hydrogenation of C–C double bonds is one of the showcase examples of the importance of homogeneous catalysis for both industry and academic research. This transformation involves the addition of molecular hydrogen to alkenes in the presence of catalytic amounts of a chiral transition-metal complex and is an atom-economical and powerful method for the synthesis of optically active compounds. Over the last decades, considerable progress has been made in this field, and now a wide range of products can be made in enantiomerically pure form by the use of catalytic systems based on combinatorial screening protocols or rationally designed (supramolecular) ligands.[1] Whereas ruthenium complexes have been demonstrated to give particularly good results in the asymmetric hydrogenation of imines and ketones, the asymmetric hydrogenation of C–C double bonds is still mainly carried out with rhodium complexes. In the latter case, coordination of the substrate to the metal catalyst needs to occur in a bidentate fashion through the double bond and a polar functional group (e.g. a carbonyl or alcohol group) for the reaction to proceed with high selectivity. Thus, these catalysts are limited to substrates with, for example, amide or ester groups next to the alkene. The hydrogenation of alkenes that do not contain such groups is still a real challenge.[2] Therefore, the development of new technologies that are suitable for these substrates has attracted recent interest.[3]

Since the pioneering work of Crabtree et al., who demonstrated the ability of an achiral iridium complex ($[Ir(pyr)(PCy_3)(cod)]PF_6$ (pyr = pyridine, Cy = cyclohexyl, cod = 1,5-cyclooctadiene)) to act as an efficient catalyst for the transformation of unfunctionalized alkenes, tremendous efforts have been made towards the asymmetric hydrogenation of such alkenes.[4] In particular, the use of chiral Ir(P,N) and Ir(P,O) complexes as catalytic precursors by Pfaltz and co-workers paved the way for the preparation of enantiomerically enriched hydrocarbons from unfunctionalized olefins.[5] However, there is still room for the development of new and efficient technologies, especially for the asymmetric hydrogenation of terminal 1,1-disubstituted alkenes bearing noncoordinating substituents. Indeed, 1,1-diaryl and 1,1-dialkyl alkenes are very challenging and highly valuable substrates.[2b,e] The corresponding chiral alkane moieties are found in various biological active compounds (Scheme 1), and new synthetic procedures that enable fast synthesis and efficient postmodification are highly desirable.[6]



Scheme 1. Examples of pharmaceutically relevant compounds containing a chiral 1,1-diaryl motif.

Until now, the enantioselectivity of the hydrogenation of 1,1-diaryl alkenes was generally ensured by the coordination of a polar directing group on one of the aryl groups in rhodium-catalyzed reactions[7] or by steric differentiation between two chemically different aryl groups in iridium-based systems.[2a,8] In both cases, the systems are of rather limited scope. Recently, a new approach was introduced in this field: the application of (transformable) directing groups remote from the alkene (Scheme 2). This directing-group-based strategy has already proved its undeniable power in the field of C–H bond transformations, in which it has been applied efficiently for the last two decades.[9] In contrast to the direct substitution of olefins with polar functional groups, a remote

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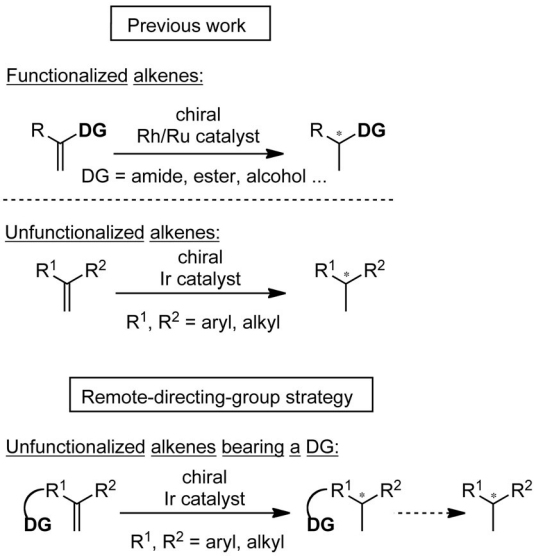
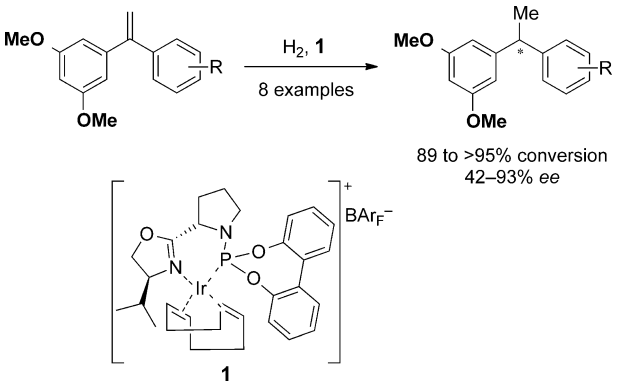
[**] Eastman Chemical Company and the Rubicon Program of the NWO are acknowledged for financial support to T.B. and R.G.-D., respectively.



Scheme 2. State of the art of the asymmetric hydrogenation of terminal alkenes (top) and the directing-group strategy (bottom).

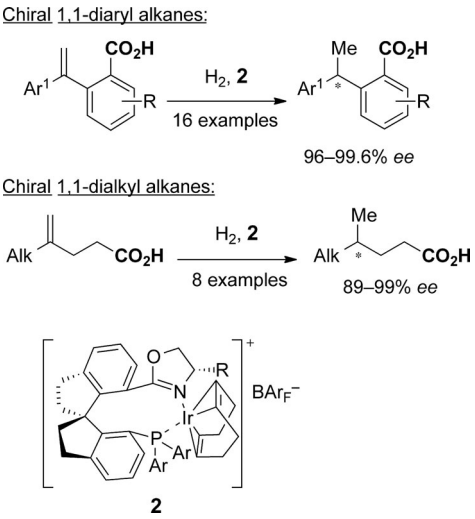
directing group (DG), generally installed on a nonpolar substituent of the alkene, can be removed after the hydrogenation event or transformed into useful functionalities by conventional methods, as was also demonstrated.

Recently, Bess and Sigman[10] demonstrated a new approach to the construction of highly enantiomerically enriched, unfunctionalized 1,1-diaryl alkane scaffolds (Scheme 3). Their strategy relies on a *meta*-substituted DG (i.e. with one aryl group bearing 3,5-dimethoxy substituents), which in the presence of the chiral, Ir(P,N)-based catalyst **1** promotes the desired asymmetric hydrogenation with the highest enantioselectivity reported so far (up to 93% *ee*).[2b,8] According Bess and Sigman, the high enantioselectivity might be attributed to a favorable π–π interaction between the methoxylated ring and the catalyst. Unfortunately, since the removal or transformation of the methoxy groups has not been reported yet, this transformation is rather limited in scope; however, the example is significant as a proof of principle for remotely directed hydrogenation reactions.



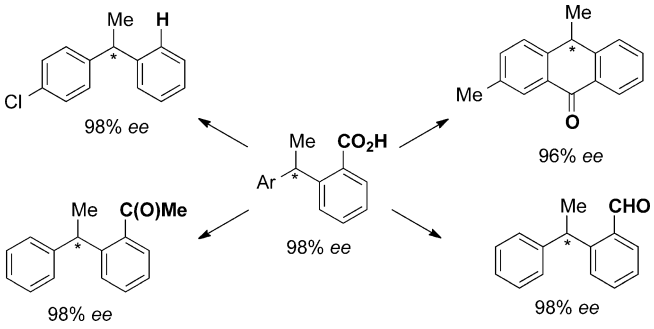
Scheme 3. Iridium-catalyzed asymmetric hydrogenation of diaryl alkenes.

The real breakthrough in this respect is the more general approach that has been nicely exemplified by Zhou and co-workers. They report the synthesis of enantiomerically enriched terminal 1,1-diaryl alkanes through an Ir-catalyzed hydrogenation reaction (Scheme 4)[11] that is directed remotely by the removable and transformable carboxy group (−CO_2H).[12] It turned out to be highly effective to induce enantioselectivity in the presence of the well-designed chiral spiro phosphine–oxazoline Ir complex **2**. A collection of terminal 1,1-diaryl alkenes bearing an *ortho*-substituted carboxy group were hydrogenated efficiently with very high enantioselectivity (96–99.6% *ee*). The system was demonstrated to even be compatible with heterocyclic cores, such as furan and thiophene moieties. Previously, Ru-catalyzed hydrogenation reactions of diaryl ketones, as developed by Noyori and co-workers, were shown to benefit from the presence of an *ortho*-substituted aryl group, which promoted high enantioselectivity.[13] In the current example reported by the Zhou research group, the coordination of the carboxy group to the Ir complex appears to play a pivotal role in the enantiodiscrimination; for example, the steric bias induced by an ester moiety is inefficient. The extension of this transformation to more challenging 1,1-dialkyl alkenes gave remarkable results. High enantioselectivities (89–99% *ee*) and excellent yields (91–97%) were observed, and thus a new synthetic pathway for the straightforward synthesis of very valuable chiral γ-methyl fatty acids was developed.[14]



Scheme 4. Iridium-catalyzed carboxy-directed asymmetric hydrogenation of 1,1-diaryl and 1,1-dialkyl alkenes.

Interestingly, Zhou and co-workers managed to readily transform the carboxylic acid group in the chiral 1,1-disubstituted alkanes at will, while retaining the enantiomeric purity (Scheme 5). A one-pot procedure—asymmetric hydrogenation followed by a decarboxylation reaction—led to chiral 1,1-diaryl alkanes without any trace of the directing group. This sequence of reactions makes this class of products now generally accessible. Additionally, the carboxy group can be converted into a ketone or aldehyde or can be before employed in an intramolecular Friedel–Crafts reaction.



Scheme 5. Examples of straightforward transformations of the DG.

Similar transformations of chiral 1,1-dialkyl alkane substrates bearing a carboxy group are possible. Notably, the same carboxylate DG group was very recently employed efficiently in a supramolecularly controlled hydroformylation reaction with high regioselectivity; further chemical transformations were also reported.[12c]

The strategy based on the use of remote directing groups in the iridium-catalyzed asymmetric hydrogenation of terminal unfunctionalized alkenes is an important breakthrough. It allows straightforward atom-economical access to highly valuable organic scaffolds and thus paves the way to industrial applications of such systems. As has been shown by the studies from Zhou and Sigman research groups, excellent enantioselectivities together with high yields are now achievable for this difficult class of alkene substrates, although turnover (activity) remains rather poor at this stage. Furthermore, removal of the carboxylate directing group and its postmodification into different functional groups with retention of enantiomeric purity have been demonstrated, even in one-pot tandem reactions. The development of new directing groups that can be introduced readily and generally and be used for further transformations after the hydrogenation is desirable and will further extend the scope and applicability of the methodology. If more of such directing groups are exploited and the activity of the catalysts is further improved, there is no doubt that this strategy will become a helpful and practical tool for transition-metal-catalyzed hydrogenation and will open new avenues for the introduction of chirality during the preparation of biologically relevant compounds.

Received: April 9, 2013
Published online: July 24, 2013

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