Asymmetric Catalysis

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Simple, but Challenging: Recent Developments in the Asymmetric Synthesis of Spiroketals**

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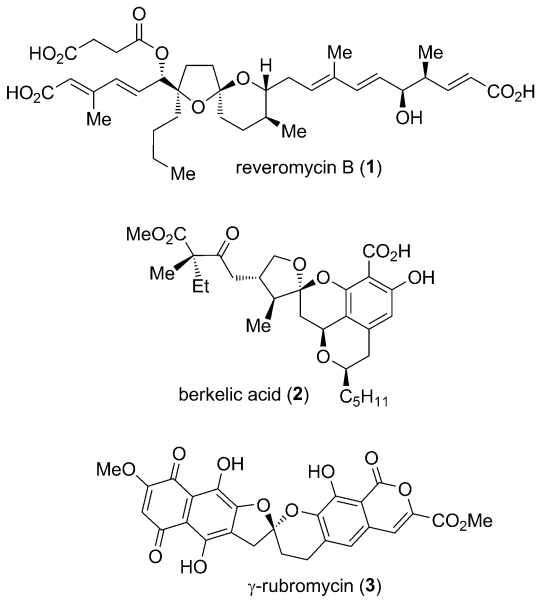
The spiroketal moiety, a structural motif frequently found in natural products, significantly contributes to the biological properties of these molecules. Compounds containing this feature range from simple chiral compounds to complex spiroketal polyketides such as reveromycin B (**1**).[1] Natural products with benzannulated spiroketals (here: aromatic spiroketals) are less common, but prominent and interesting examples, such as berkelic acid (**2**) and γ-rubromycin (**3**), are known (Scheme 1). Two recent reviews[2] provide insight into successfully completed total syntheses of natural products that contain aromatic [5,5]-, [5,6]-, and [6,6]-spiroketal units as key structures.

In this context, enantiomerically pure compounds could be obtained exclusively through diastereoselective spiroketalizations (or equivalent reactions) starting from chiral precursors; in other words, the stereoselective synthesis becomes significantly more challenging when the spiroketal carbon of the natural product is the only stereogenic center. In the case of γ-rubromycin the common approaches, such as the acid-induced spiroketalization of dihydroxy ketones[3] and alternative strategies based upon aromatic Pummerer-type reactions[4] and the [3+2]-cycloaddition,[5] provided the target, but only as a racemate. An asymmetric entry to γ-rubromycin is yet unknown and until recently methods for the direct catalytic enantioselective spiroketalization starting from achiral substrates have not been described.



Scheme 1. Natural products containing [5,6]-spiroketal units.

Ding et al. now report the first enantioselective synthesis of aromatic spiroketals.[6] Inspired by research from the Bolm[7] and Hou groups[8] and based on their own experiences with iridium(I)-catalyzed hydrogenations of ketimines[9] and of α-aryl β-substituted acrylic acids,[10] the authors explored the catalytic asymmetric hydrogenation of α,α′-bis(2-hydroxyarylidene)ketones of type **4**, followed by an immediate diastereoselective cyclization to provide the aromatic [6,6]-spiroketals **6** (Scheme 2).

This transformation is initiated by the enantioselective reduction of the prochiral α,β-unsaturated ketone **4** to the chiral *trans*-2,6-disubstituted cyclohexanone **5**. For this purpose, iridium(I) complexes of phosphine–oxazoline ligands [(P,N)-hybrid ligands] proved to be efficient catalysts; in particular the (*S*,*S*)-spinPHOX ligand (Scheme 2) provides excellent enantioselectivities and yields. The instantaneous spiroketalization proceeds in a highly diastereoselective fashion and is probably catalyzed by an iridium(III) species which is formed with hydrogen in situ. This assumption is supported by control experiments. In an interesting example, Ding et al. describe the subsequent reaction of the dibromo-substituted derivative **7** which leads to the new chiral diphosphine ligand **8** (Scheme 3). This type of ligand based upon a spiro-2,2′-bichromane structure has already been applied successfully in asymmetric transformations.[11]

The procedure guarantees excellent results (high yields of spiroketals with high enantio- and diastereoselectivities), but the reaction still seems to be strictly limited to cyclic ketones as suitable substrates. The spiroketalization of α,α′-bis(2-hydroxyaryliden)ketones that do not have a cyclic backbone or further substituents in the α- and/or β-position results in racemic products since an achiral intermediate is generated after the hydrogenation.

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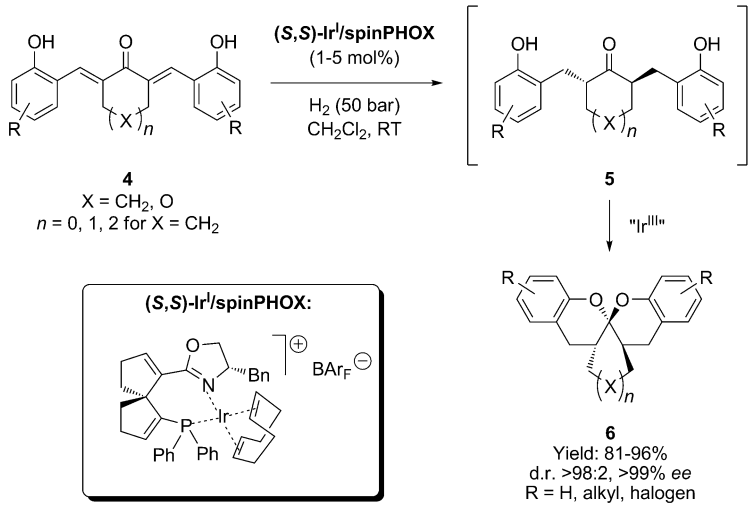
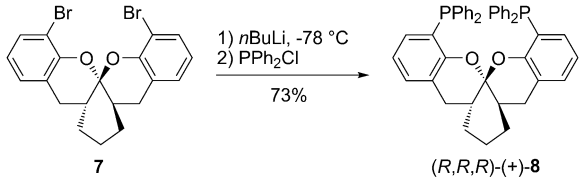


Scheme 2. Synthesis of chiral, aromatic spiroketals **6** by Ding et al. BAr_F: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

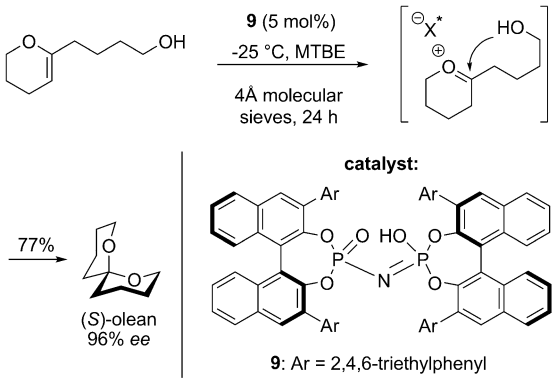


Scheme 3. Synthesis of enantiomerically pure diphosphine ligand **8**.

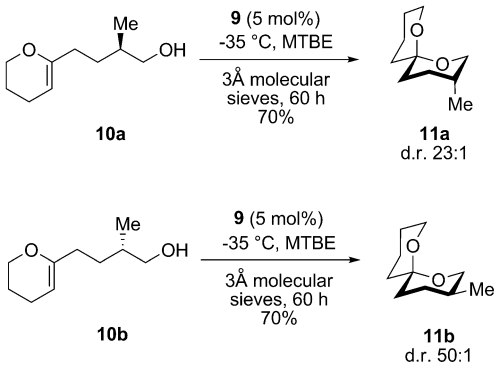
The very first example of a truly catalytic asymmetric spiroketalization starting from achiral substrates has been reported recently by List and Čorić.[12] In their pioneering studies they utilize a chiral binol-based C_2-symmetric imidodiphosphoric acid as the catalyst, which converts hydroxyalkyl-substituted enol ethers to spiroketals with high enantiomeric excess. An impressive example is given in the synthesis of the pheromone olean in enantiopure form (Scheme 4).

The asymmetric induction from the catalyst to the substrate arises from the facial differentiation of the oxocarbenium ion intermediate by the imidodiphosphoric acid **9**. The decisive factor is the location of the aryl substituents at 3- and 3′-positions of the two identical binol units; this arrangement ensures that the conformation of the *O*,*O*-*syn*-imidodiphosphate anion is fixed, providing a molecular structure with high rigidity and a suitable cavity. A crystal structure analysis of the imidodiphosphoric acid **9** suggests that the catalytic site, like that of enzymes, is hidden deep inside a "pocket". This type of catalyst design is necessary to guarantee a high enantioselectivity.

In addition to the above-mentioned example of (*S*)-olean, diverse spiroketals are accessible by varying the ring size of the enol ether and the chain length of the attached hydroxyalkyl group. Remarkably, substituted substrates such as enolethers **10a** and **10b** were efficiently cyclized in high yields and excellent diastereoselectivities (Scheme 5). In this case the catalyst controls the absolute configuration at the spiroketal carbon, even when this leads to the thermodynamically less favored product; thus **10a** is converted into the thermodynamically less stabilized spiroketal **11a** with the methyl group in the axial position. Syntheses of aromatic spiroketals have not been described yet; however, this concept should also be applicable for this class of products.[13]



Scheme 4. Brønsted acid catalyzed asymmetric spiroketalization; MTBE: *tert*-butyl methyl ether.



Scheme 5. Examples of the diastereoselective spiroketalization of chiral substrates utilizing catalyst **9**.

The highlighted publications clearly illustrate the challenges associated with the synthesis of (aromatic) spiroketals in enantiomerically pure form. The Ding and List groups offer elegant solutions by taking advantage of modern transition-metal catalysts and organocatalysis, respectively. It is expected that these methods will find their way into the field of total synthesis. Future developments are eagerly awaited.

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