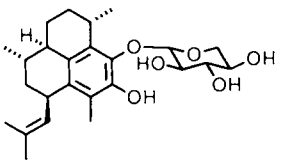
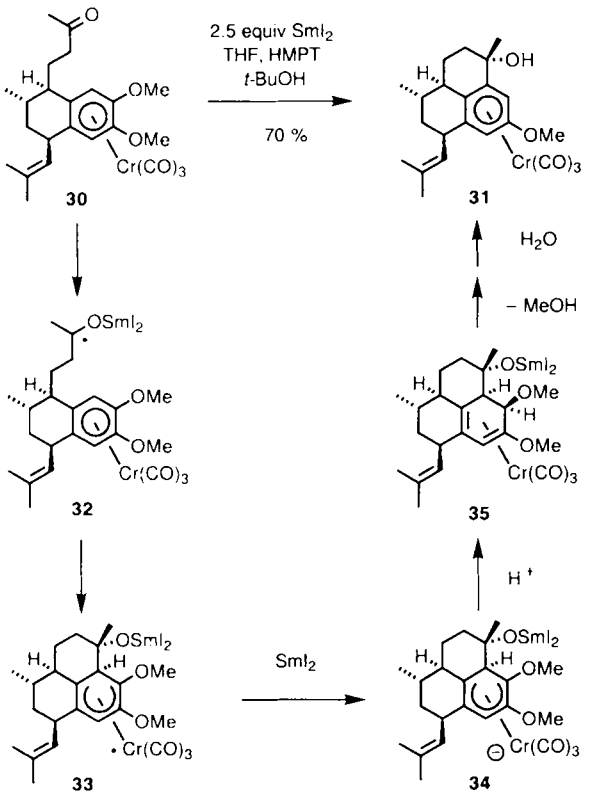


pseudopterosin A (**29**)



The present selection of natural product syntheses with radical reactions as key steps demonstrates the extraordinary potential applications of modern radical chemistry. However, one limitation is evident: four out of the five reaction sequences presented involved an intramolecular cyclization reaction.[10] Intermolecular radical bond formations with high yields and stereoselectivities are still very rare in the total synthesis of bioactive compounds. One exception is the camptothecin synthesis by Curran et al. However, progress in acyclic stereoselection of radical reactions[11] should soon help to formulate new solutions for these synthetic challenges.

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Keywords: natural products · radical reactions · tandem reactions · total syntheses

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Enantioselective Catalytic Hydrogenation

Judith Albrecht and Ulrich Nagel*

Enantioselective catalysis is one of the most important tools in asymmetric synthesis.[1, 2] With its assistence biologically active substances can be prepared in enantiomerically pure form—this purity can be a crucial factor with pharmaceutical products. In the field of crop protection the use of enantiomerically pure compounds provides irrefutable advantages for both economic and ecological reasons.[3, 4]

Enantioselective transition metal catalyzed hydrogenation has an important place among the methods of asymmetric synthesis. A large range of substrates can be enantioselectively hydrogenated in this way, which is extremely important for the preparation of natural and also nonnatural amino acids, because it enables the directed synthesis of all possible amino acid derivatives from the many prochiral enamides and ketones. Recently great progress has been made in this field. Very high *ee* values are achieved, and even sterically demanding substrates like β,β-disubstituted enamides are able to be hydrogenated in good optical yield.[5, 6]

Since the beginning of the 90's Burk et al. have been exploring the development of novel electron-rich phosphane ligands that give powerful catalysts for enantioselective hydrogenation on complexation with rhodium.[7] The ligands they use each contain two phospholanes *trans*-substituted in 2,5 position, whose

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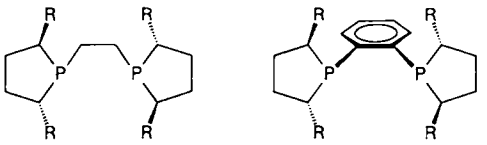
phosphorus atoms are linked together through different groups as backbone. The carbon atoms adjacent to the phosphorus atoms are chiral and in these catalysts are situated in the immediate vicinity of the rhodium atoms (Scheme 1).



BPE DuPHOS

Scheme 1. The bisphospholane ligands BPE and DuPHOS; R = Me, Et, *n*Pr, *i*Pr (to give Me-, Et-, *n*Pr-, and *i*Pr-BPE or -DuPHOS).

Initially the phospholanes were synthesized by derivatization of homochiral 1,4-diols with mesyl chloride. The dimesylates were then transformed into the 2,5-disubstituted phenylphospholanes with dilithiumphenylphosphide. The phenyl group was cleaved with pure lithium metal, and the resulting lithium phosphide could then be converted into the bridged system with 1,2-dichloroethane, ethyleneglycoldi-*p*-tosylate, or 1,3-dichloropropane. The yields with this synthetic route were moderate and depended strongly on the purity of the lithium metal.[8]

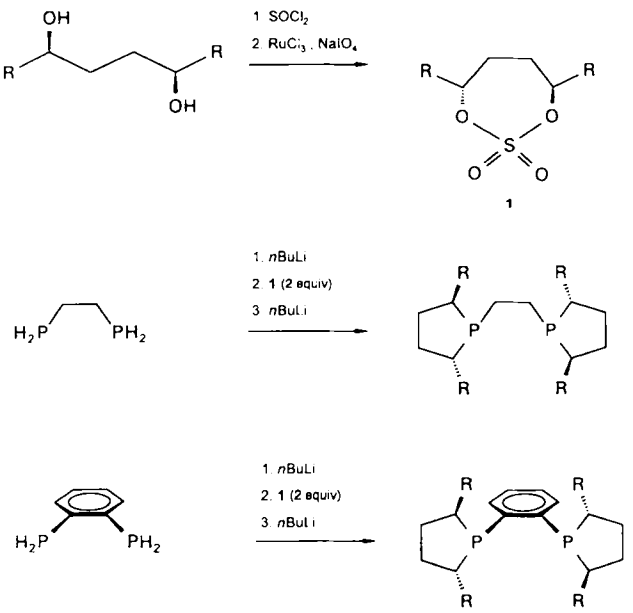
A later optimized synthesis also starts from the 1,4-diols. They are then converted into cyclic sulfates with thionyl chloride on mediation of ruthenium chloride and sodium periodate. The sulfates are transformed with dilithiumbis(phosphido)-ethane into bis(phospholanyl)ethane ligands (BPE) or with dilithium-1,2-bis(phosphido)benzene into a bis(phospholanyl)-benzene (DuPHOS) ligand. Ring closure to form phospholanes is achieved by addition of *n*BuLi[9] (Scheme 2).

The differently substituted BPE and DuPHOS rhodium complexes were applied in the hydrogenation of *N*-acetyl enamines. Of the BPE ligands, the ethyl-substituted derivative gave the highest *ee* values (93% for methyl α-acetylaminocinnamate and 98% for methyl α-acetylaminoacrylate). Higher enantioselectivities were achieved with the DuPHOS ligands. Under optimized conditions some systems afforded *ee* values of over 99%. In particular the sterically demanding *n*Pr-DuPHOS gave *ee* values of 99.8% (enantiomer ratio 1000:1).

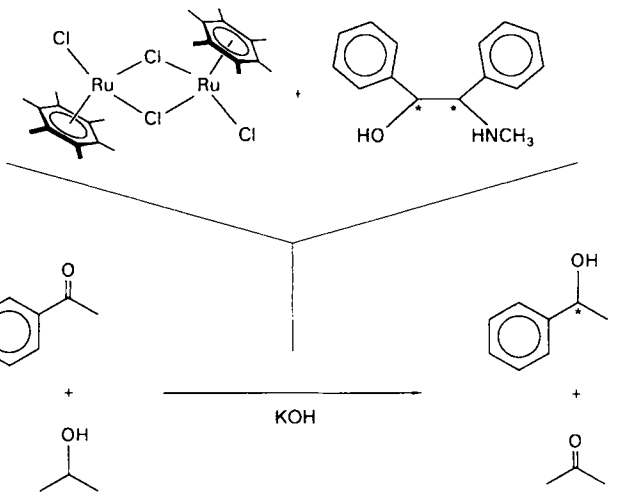
In all enantioselective hydrogenations the ability of the substrate to form a chelate ring with the catalyst is extremely important. For this reason the enantioselective reductive amination of ketones is always particularly difficult, because these compounds usually do not have a structure suitable for the required chelation. Burk et al. circumvent this problem by reversible derivatization. The ketones are converted into *N*-acetylhydrazones, whose structures resemble those of enamides.[10] The C–N double bond can then be hydrogenated by *n*Pr-DuPHOS–rhodium with *ee* values almost as high as those for C–C double bonds of enamines. The *N*-acetylhydrazines obtained thus can either be transformed into the free hydrazines by acid hydrolysis or into amines by treatment with samarium diiodide. In this way a large number of ketones can be reductively aminated.[11]

To hydrogenate prochiral ketones to the corresponding chiral alcohols, Noyori et al. have developed ternary catalyst systems from $[RuCl_2(binap)(dmf)_n]$, a chiral diamine, and KOH.[12, 13] By this route methyl(1-naphthyl)ketone can be hydrogenated to 1-(1-naphthyl)ethanol with $[RuCl_2(binap)(dmf)_n]$, 1,2-diphenylethyldiamine, and KOH in the ratio 1:1:2 in 2-propanol (substrate:catalyst = 500:1, 4 bar H_2, 28 °C, 6 h) in greater than 99% yield with 97% *ee*.

Other sources of hydrogen can be used instead of elemental hydrogen gas. In transfer hydrogenations a secondary alcohol has been employed as hydrogen donor. Noyori et al. have also made advances in this field. They use a catalyst system from $[RuCl_2(\eta^6\text{-mesitylene})]_2$, *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine, and KOH in 2-propanol. At room temperature acetophenone can be reduced in 15 h with this complex prepared in situ (substrate:catalyst = 200:1) to 1-phenylethanol in 95% yield with an optical purity of 97%.[14] Catalyst systems with a β-amino alcohol as auxiliary are faster, as shown by the reduction of acetophenone to 1-phenylethanol under otherwise identical conditions with $[RuCl_2(\eta^6\text{-hexamethylbenzene})]_2$, 2-methylamino-1,2-diphenylethanol, and KOH within as little as 1 h in 94% yield and 92% *ee* (Scheme 3).[15]



Scheme 2. Synthesis of BPE and DuPHOS ligands.

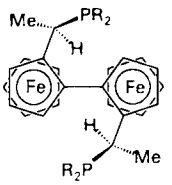


Scheme 3. Transfer hydrogenation of acetophenone.

The *N*-acetylhydrazones used by Burk et al. are ketone derivatives, and their structures therefore correspond to those of the β,β-disubstituted *N*-acetylaminoacrylic acids. This and the finding that both the (*E*)- and the (*Z*)-enamides are hydrogenated with almost the same enantioselectivity by the BPE and DuPHOS complexes prompted them to investigate the ability of the phospholane ligands to enantioselectively hydrogenate β,β-disubstituted *N*-acetylaminoacrylic acids.[5]

Attempts to use the ligands Et-, *n*Pr-, and *i*Pr-DuPHOS, which were most successful for the *N*-acetyl enamines, gave unsatisfactory results: the *ee* values were 74, 45, and 14%, respectively. In supercritical CO_2 as solvent[16] they improved to 90%. The use of supercritical CO_2, however, puts a greater demand on the hydrogenation apparatus than conventional conditions, since it must be able to withstand high pressures. The temperature must also be precisely controlled, because in supercricital systems merely a small temperature difference can lead to enormous effects.

The *trans* chelate ligands developed by Ito et al. are also used for enantioselective hydrogenation of β,β-disubstituted *N*-acetylaminoacrylic acids.[6] These ligands fall into the class of TRAP ligands (Scheme 4, TRAP = 2,2″-bis[1-(dialkylphosphanyl)-ethyl]-1,1″-biferrocene), with which good *ee* values are achieved. Methyl α-*N*-acetylamino-β,β-dimethylacrylate can be hydrogenated with Bu-TRAP at a catalyst:substrate ratio of 1:1000 in 24 h (15 °C, 1 bar H_2) to form the corresponding propane carboxylic acid in 88% *ee*.



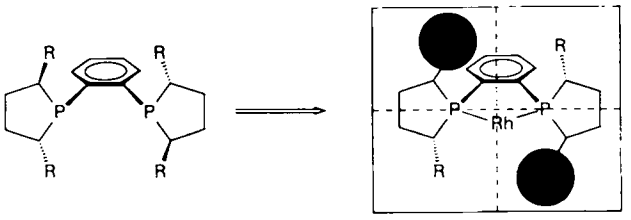
Scheme 4. Ito's TRAP ligand.

Further progress in the hydrogenation of β,β-disubstituted *N*-acetyl enamines was made with the sterically less hindered Me-DuPHOS–rhodium catalyst. In this system an *ee* value of 92% was obtained.[5]

The best enantioselectivities till now have been reached with the Me-BPE ligand. With this ligand a large variety of β,β-disubstituted *N*-acetyl enamines were hydrogenated with very high *ee* values of over 99% in some cases. For a catalyst:substrate ratio of 1:500 under mild conditions (25 °C, 6 bar H_2) β-methyl- and β-ethylphenylalanine derivatives could be prepared from the corresponding β,β-disubstituted *N*-acetylaminoacrylates in 12–24 hours with optical yields of 99.4 and 99%, respectively.

The Pr-DuPHOS ligand is one of the best ligands for the hydrogenation of sterically less congested substrates, whereas for the sterically more demanding β,β-disubstituted compounds the ligand Me-BPE is the better choice. The astoundingly different behavior of derivatives of these catalysts is hard to predict, yet because of the opportunities for variation in the synthesis of the bisphospholanes, the broadest possible tailoring of the ligands to a problem at hand is assured.

An old but graphic picture to explain the enantioselectivities with different ligands is that of the blocked quadrants[17] (Scheme 5). The rigid benzene ring in the backbone of the



Scheme 5. Blocked quadrants.

DuPHOS ligands blocks two diagonally oriented quadrants at the metal atom through the substituents on the phospholane ring. The bulkier the substituent and the more rigidly it is held in its position, the better the quadrants are blocked. For most of the sterically less hindered substrates like β-monosubstituted acetylaminoacrylic acids the optimum is reached with the *n*Pr-DuPHOS ligand. The ligand in the catalyst may not be so bulky that the binding of the substrate is overly restricted. Thus the *ee* values for hydrogenations with the bulkier *i*Pr-DuPHOS–rhodium catalyst decrease.[9]

In the case of the tetrasubstituted acrylic acids the rigid DuPHOS ligands block both diagonally oriented quadrants so severly that the larger space requirements of these substrates cannot be accommodated. Here the more flexible Me-BPE ligand with its smaller methyl groups performs better.

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Keywords: asymmetric syntheses · enamides · hydrogenations · phosphane ligands · supercritical phases

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