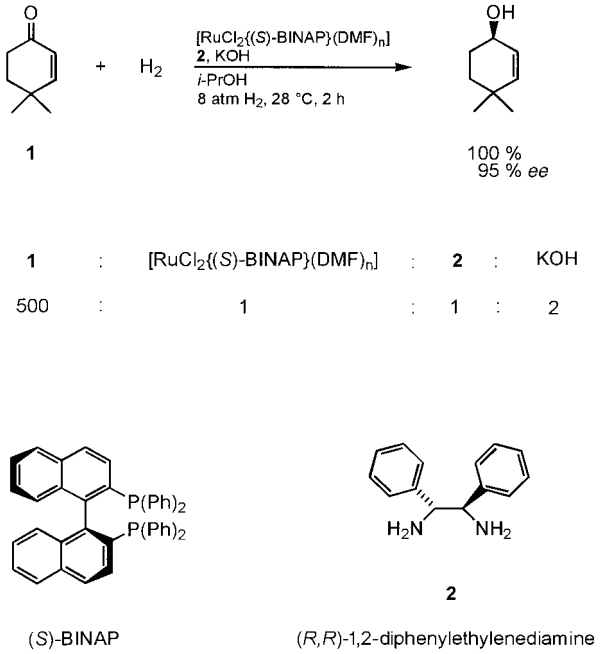
Highly Enantioselective Complex-Catalyzed Reduction of Ketones—Now with Purely Aliphatic Derivatives Too

Volker Fehring and Rüdiger Selke*

The research group of Zhang at Pennsylvania State University has climbed a mountain that had long defied all attempts at scaling its peak—the complex-catalyzed, highly enantioselective (*ee* values of over 90%) hydrogenation of purely aliphatic ketones.[1] Such high *ee* values have up till now remained the exclusive domain of enzymatic methods.[2]

It has long been possible to asymmetrically hydrogenate a wide range of functionalized ketones with selectivities of over 90% *ee*. Thus, pharmaceutically important 1,2-amino alcohol derivatives have been available since 1979 with over 95% *ee* through the hydrogenation of amino ketones. This was achieved by Hayashi et al.[3] with the use of planar chiral ferrocenebis(phosphanyl)rhodium(I) catalysts and above all by application of the *control concept* developed by Achiwa et al.[4] with BCPM rhodium(I) catalysts (BCPM = (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(dicyclohexylphosphanyl)-2-(diphenylphosphanylmethyl)pyrrolidine).[4b] Very high turnover numbers (100000) can thus be achieved. Likewise, α- and β-ketocarboxylic acid derivatives have been reduced (>90% *ee*) to the hydroxy acids or corresponding derivatives with high selectivity;[4a, 5, 19a] the most impressive results were obtained with chiral, modified heterogeneous catalysts.[6] Since the pioneering studies of Noyori et al. with BINAP–ruthenium(II) complexes[7] (BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, see Scheme 1), the range of ketones which can be homogeneously hydrogenated with *ee* values of well over 90% has been expanded to encompass among others γ-keto esters, hydroxy ketones, α- and β-diketones, and even phenyl thioketones.[7f] Also the important regioselective hydrogenation of unsaturated, and even cyclic, ketones such as **1** was possible with 95% *ee* (Scheme 1).[7d, e] In this case, the otherwise preferred hydrogenation of the olefinic double bond[7g] is completely suppressed by the addition of a chiral diamine such as (*R*,*R*)-1,2-diphenylethylenediamine (**2**), which serves as a selectivity-promoting modifier (Scheme 1). Moreover, Noyori et al. have recently shown that the selecting power of the enantiomerically pure diamine **2** is alone sufficient for a successful reaction, as the enantioselectivity



Scheme 1. Regioselective hydrogenation of unsaturated ketones.

falls only from 96 to 95% if racemic TOLBINAP[7h] is used instead of (*R*)-TOLBINAP (TOLBINAP is a BINAP derivative in which the four phenyl groups attached to the phosphorus atoms are replaced by four *p*-tolyl groups).

The transformation of unfunctionalized alkyl aryl ketones such as acetophenone and its analogues to the corresponding chiral alcohols with enantioselectivities of around 95% was for a long time possible only by asymmetric hydrosilylation[8] or hydroboration.[9] However, in 1995 this reaction was accomplished by activation of BINAP–ruthenium catalysts with chiral diamines and KOH.[10] In its optimized form the reaction needs less than 10^{-4} mol% of catalyst.[10b] Similarly high selectivities were also reported for cyclic alkyl aryl ketones with BINAP–iridium catalysts.[11] Use of sodium borohydride as the reductant and the cobalt catalysts **3** with tetradentate ligands derived from Schiff bases afforded reduction of ketone **4** with 94% *ee*. However, the corresponding reaction with acetophenone was unsatisfactory with only of 68% *ee*.[12]

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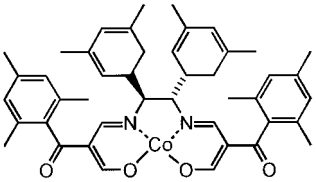

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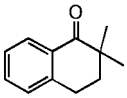

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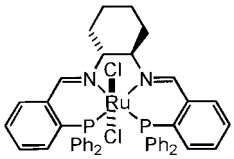
A successful approach in the field of transfer hydrogenation with formic acid or isopropyl alcohol as the hydrogen source has been developed by Noyori[13a] through the use of ruthenium catalysts containing chiral $\widehat{NP}$ chelating ligands such as **5** or monosulfonated bis(amine)s such as **6**. This breakthrough is particularly significant in the case of alkyl aryl ketones or ketones with triple bonds in the α position.[13b] The



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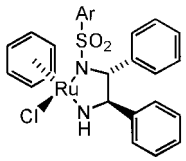

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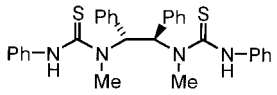
excess hydrogen pressure normally necessary for ketone hydrogenations is avoided here by the high concentration of the hydrogen donor. Enantioselectivities of between 95 and 99% are afforded in most cases for aryl alkanols; such values can otherwise be obtained only with microbiological processes.[14]

The number of publications describing new ligands that allow the transfer hydrogenation of aromatic ketones with over 90% *ee* has grown in leaps and bounds since 1996.[15] In these reactions the use of ruthenium[15a–f] and iridium[15g] as the catalytically active metals has recently been augmented by the use of phosphorus-free ligands such as chiral diamines, amino alcohols, and bis(thiourea)s such as **7**.[15a, e–g] A ruthenium-catalyzed transfer hydrogenation with 92% *ee* has even been reported for the aliphatic ketone pinacolone (*tert*-butyl methyl ketone).[16]



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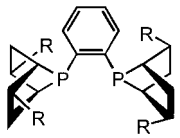
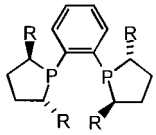
One problem that remains unsolved is the complex-catalyzed enantioselective hydrogenation of dialkyl ketones with dihydrogen gas, as these substrates lack the aryl substituent or second functional group necessary for effective enantiofacially selective binding to the catalyst. Corey et al. nevertheless succeeded in reducing pinacolone, in which the steric requirements of the methyl und *tert*-butyl substituents differ quite distinctly, by the hydroboration method with 97% *ee*.[9] By contrast, the straight-chain octan-2-one gave an *ee* value of only 72%,[17] compared 94% *ee* with an alcohol dehydrogenase.[2]

A particularly successful approach to the catalytic hydrogenation of dialkyl ketones with hydrogen has been the use of the heterogenous contact catalyst system—Raney nickel chirally modified with tartaric acid.[18] Here too, selectivity is enhanced by branching of the alkyl substituent in the alkyl methyl ketones (e.g., 85% *ee* for the hydrogenation of isopropyl methyl ketone). With straight-chain ketones the highest *ee* values were achieved for hexan-2-one and octan-2-one (80%). Catalyst selectivity was optimized by the use of pivalic acid as a modifier, which through association clearly blocks one side of the chirality-inducing tartaric acid molecules on the surface of the nickel. Owing to the sterically demanding *tert*-butyl group of the pivalic acid, the range of options for coordination of the ketone to the tartaric acid in the transition state is limited. It is, of course, perfectly conceivable that this differentiation effect is particularly pronounced for alkyl methyl ketones and decreases upon replacement of the methyl group with a larger alkyl moiety.

Ligands of type **8**, known as PennPhos, have given new impetus to the rhodium-catalyzed homogeneous hydrogenation of prochiral ketones.[1] In **8** the favorable properties of the



PennPhos **8a** R = Me
8b R = *i*Pr



DuPhos **9**
(R = Me, Et, *n*Pr, *i*Pr)

strongly basic DuPhos ligands **9**, developed by Burk et al.,[19] are cleverly enhanced by the incorporation of additional ring-forming bridges into the molecule, in accordance with the established principle of increasing the rigidity in the backbone. This at the same time increases the spatial requirements of the ligands. For the hydrogenations with **8** the enantiomeric excesses obtained are likewise optimized by the use of nonchiral modifiers such as bromides and weak bases. A remarkable feature of this reaction is that bases such as 2-methylimidazole and 2,6-lutidine, if added in substoichiometric amounts to the rhodium catalyst, achieve very similar increases in selectivity, whereas if equimolar quantities are used (base/rhodium catalyst: 1/1) the results obtained differ dramatically (1% *ee* versus 95% *ee*, (*S*)-alcohol). Use of triethylamine as the added base even yields the *R* enantiomer. The turnover rate also shows optima that are dependent on the ratio of base to rhodium catalyst. This is viewed by the authors as an opportunity to improve the still unsatisfactory length of time required for hydrogenations with the PennPhos–rhodium catalyst, which in some cases is as long as several days at 30 atm hydrogen pressure and room temperature.

The influence of the alkyl substituents in the substrate on the enantioselectivity of the hydrogenation (Table 1) corresponds to experience from experiments with modified Raney nickel.[18] According to these, for purely aliphatic ketones the highest enantioselectivities are achieved for methyl ketones with a branched-chain second alkyl substituent. The value of 75% *ee* obtained with the straight-chain hexan-2-one is, to the best of our knowledge, in any case better than anything achieved to date with nonenzymatic systems and homogeneous catalysis. Higher selectivities have been reported for reductions with stoichiometric amounts of chiral borohydrides (e.g. 80% *ee* for the reduction of octan-2-one).[20]

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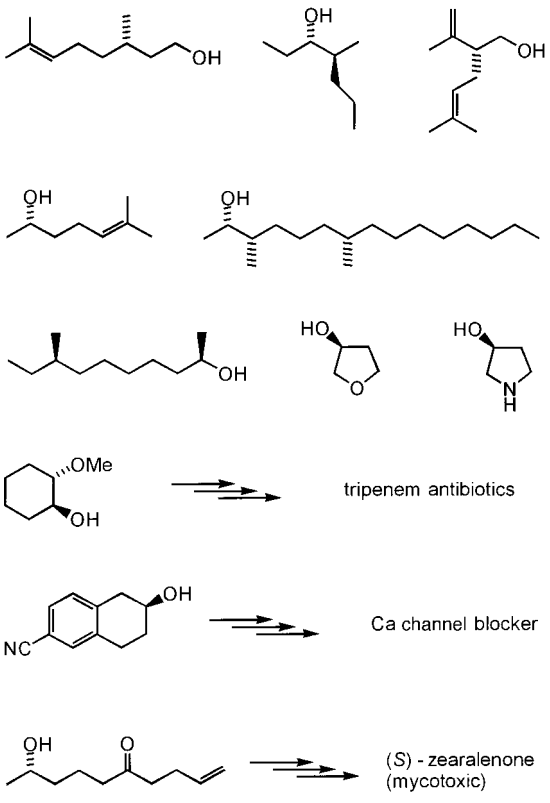
Table 1. Enantioselectivities for the hydrogenation of simple ketones RCOR′.[a]

R	R′	*ee* (*S*) [%]
*t*Bu	Me	94
C_6H_{11}	Me	92
*i*Pr	Me	84
*n*Bu	Me	75
Ph	Me	95 (without KBr)
Ph	Et	93
Ph	*i*Pr	72

[a] With 0.5 mol% $[Rh(cod)Cl]_2$, **8a**, lutidine, and KBr under 30 atm H_2.[1]

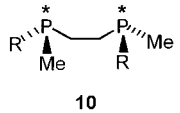
For alkyl aryl ketones, the use of the novel PennPhos rhodium catalyst afforded enantioselectivities of over 90%, such as are routinely obtained by transfer hydrogenation,[13] only for alkyl groups up to C_2. This is in contrast to microbial reductions, where the selectivity rises with the number of carbon atoms in the alkyl group.[14] A recent report describes a most spectacular inversion of selectivity for a novel ruthenium-catalyzed transfer hydrogenation of alkyl phenyl ketones with use of the bis(thiourea) ligand **7** derived from (*R*,*R*)-1,2-diphenylethylenediamine.[21] In this reaction the following enantioselectivities were obtained as a function of the alkyl group in the substrate molecule: Me: 89%, (*S*); Et: 91%, (*S*); *i*Pr: 94%, (*S*); *t*Bu: 85%, (*R*). By ordering the substrates according to the magnitude of the selectivities obtained, other studies have likewise demonstrated a marked dependence on the structure of the catalyst.[10]

The significance for industrial processes is clear. Scheme 2 shows several examples from a survey recently published by Noyori[7c] of optically active alcohols that can be used to synthesize biologically important chiral compounds below along with some of relevance to the pharmaceutical industry.[22] Pheromones constitute a particularly diverse family of chiral aliphatic alcohols.[23]



Scheme 2. Optically active alcohols that can be used to synthesize biologically important chiral compounds.[7c, 22]

Finally, the bis(trialkylphosphane) ligands **10** developed by Imamoto et al. may, on account of their high basicity, also be suitable for the hydrogenation of ketones. Use of these



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10	R
a	*t*Bu
b	Et_3C
c	1-adamantyl
d	C_5H_9
e	C_6H_{11}

ligands, which contain chiral phosphorus centers, affords enantiomeric excesses of over 99% for the rhodium(I)-catalyzed hydrogenation of *N*-acyl-dehydroamino acids.[24] The tetrasubstituted substrates, which are generally difficult to hydrogenate enantioselectively, are of particular interest. The partially reversed orders of selectivity for the five ligands described leads us to suspect that high enantiomeric excesses may also be possible for the reduction of ketones. Further advances are conceivable by combining the methods developed by the research groups of Noyori and Zhang, with the use of bases as modifiers.

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Metal Ions as Co-Inhibitors of Serine Proteases: A New Approach in the Search for Specific High-Affinity Ligands

Tanja Schirmeister*

Serine proteases are key enzymes for a variety of biological processes and are therefore of great importance in the design of new drugs.[1] The trypsin-like proteases of the blood-clotting cascade, thrombin and factor Xa, are of particular interest in this context.[2] A common characteristic is their specificity for basic amino acids in P1.[3] Apart from trypsin, the proteases of fibrinolysis (plasmin, t-PA, urokinase),[4] those of the complement system (factors C1r, C1s),[5] and the mast-cell tryptase[6] belong to this family. Leukocyte elastase is also of therapeutic interest, which, although it uses the same hydrolysis mechanism, possesses a small hydrophobic S1 pocket and thus exhibits only P1 specificity for the short-chain amino acids alanine and valine.[7] Pathological processes for which serine protease inhibitors could be of therapeutic value include blood-vessel diseases (thrombin), tumors (plasmin, urokinase), infectious processes and autoimmune diseases (tryptase, complement proteases), lung emphysema (elastase), and pancreatitis (trypsin).[1]

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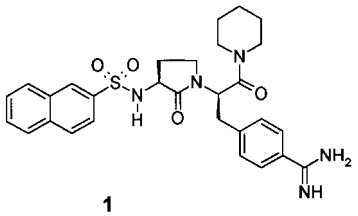
Up to now, there were three approaches to developing inhibitors for trypsin-like proteases which differed in the type of reaction between the inhibitor and the active site. Compound **1** is one of numerous benzamidines which employ their



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positively charged amidinium group to occupy reversibly and noncovalently the S1 pocket of the enzymes; the S1 pocket carries a negative charge due to the amino acid Asp 189.[8] The petidyl aldehyde GYKI 14766 (*N*-Me-D-Phe-Pro-Arg-H),[9] a potent thrombin inhibitor, additionally reacts reversibly with the serine residue at the active site to yield a hemiacetal. Irreversible inhibitors can be found, for example, in the group of peptidyl chloromethyl ketones (e.g. D-Phe-Pro-Arg-CH_2Cl).[9]

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