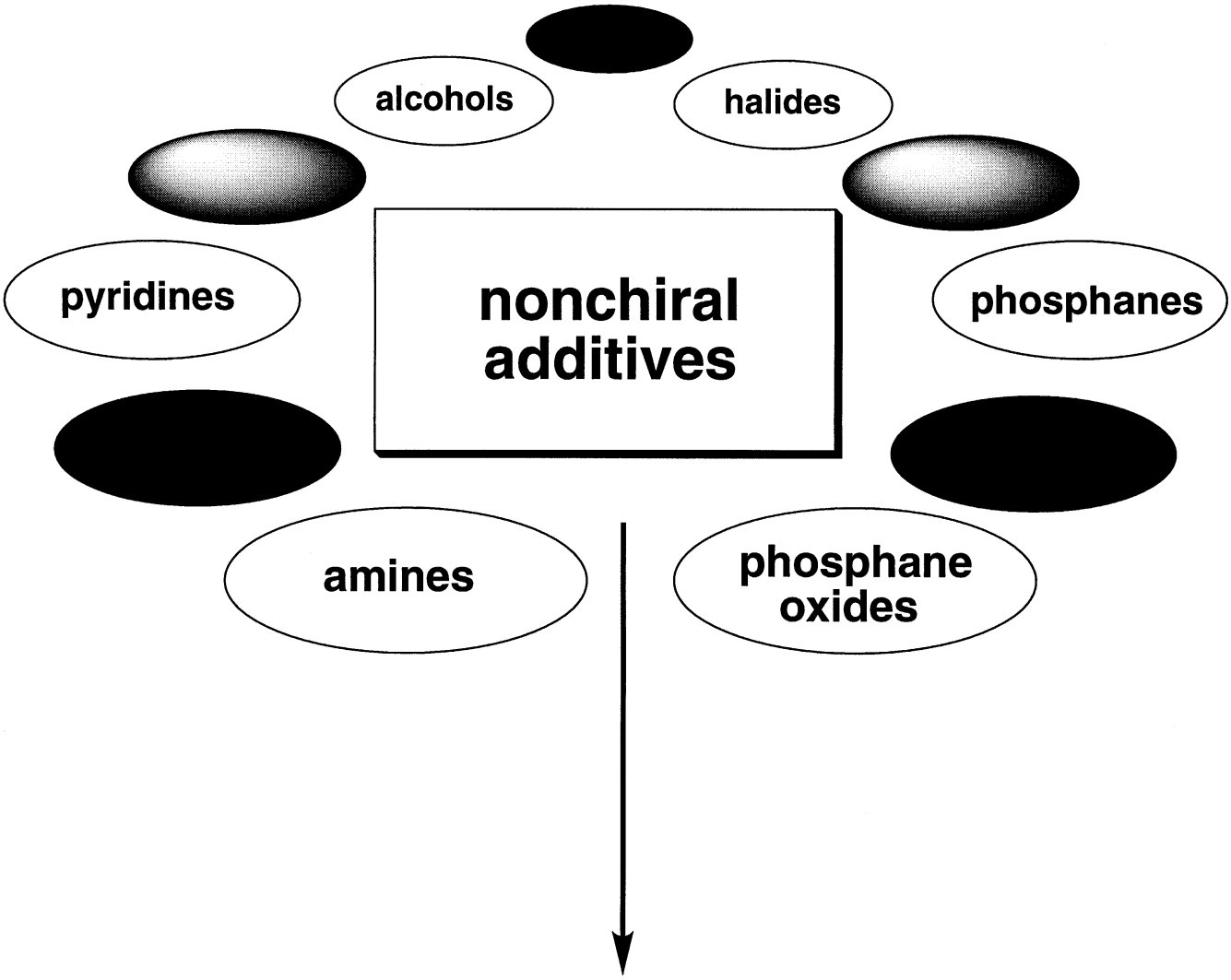
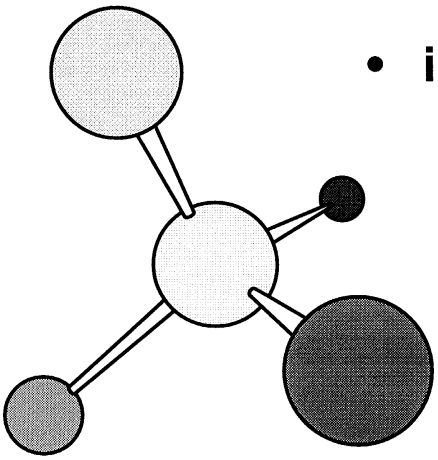


improved asymmetric catalysis



- increased stereoselectivity
- increased yields
- faster conversion
- modified reaction pathway

Towards Perfect Asymmetric Catalysis: Additives and Cocatalysts

Erasmus M. Vogl, Harald Gröger, and Masakatsu Shibasaki*

The multiplication of chiral information is one of the most important tasks in organic chemistry. Perhaps the most elegant way to achieve this is by chiral catalysis. Although organic chemists developed a variety of asymmetric catalytic reaction systems, in many cases the efficiency of the catalysts (substrate/catalyst ratio, turnover number (TON), turnover frequency (TOF)) is not yet high enough for industrial applications. Asymmetric catalytic systems are often very sensitive to small changes in reaction conditions. As a result several research groups have recognized that in many cases the addition of small (usually also catalytic) amounts of very simple achiral compounds can be beneficial for the yields *and* enantioselectivities obtained. This review intends to summarize this recent trend with experimental results from various laboratories covering a number of organic reactions and additives. In some cases a variety of similar additives was carefully investigated with respect to achieving maximum selectivity. The success of the strategy can be recognized by a comparison of the results obtained with and without the additives.

Keywords: additives · asymmetric catalysis · asymmetric synthesis · synthetic methods

1. Introduction

Over the last few years the organic chemist has greatly benefited from asymmetric catalysis, which has not only allowed convenient access to chiral compounds, but has also produced a number of efficient asymmetric reactions.[1] Nevertheless, transferring asymmetric catalytic methods to an industrial scale is unfortunately still a difficult and sluggish process. More or less successful applications of homogeneous catalytic asymmetric methodologies in industrial chemistry have only been reported for hydrogenations,[2] isomerizations,[3] cyclopropanations,[4] and epoxidations.[5] Although very often enantioselectivities of 90 to 95% *ee* have been achieved for a variety of transformations in the research laboratory, this is usually not sufficient for industrial needs, particularly when it comes to pharmaceutical intermediates and products. For example, the certification of a pharmaceutical product requires compounds to have an enantiomeric purity of 99% or more.[6] And even if such a high enantioselectivity is not required in the case of, say, pesticides, the catalyst productivity, catalyst activity, and catalyst stability can be even more important.

"How to make good asymmetric catalysis perfect" must therefore be the main concern for everybody, not only industrial chemists. Besides a subsequent (and expensive) purification step, by crystallization or separation of diastereomers, several interesting methodologies for optimization of chiral catalysis have recently been published. The underlying basic concept has already been successful in "classic industrial chemistry" for the optimization of yields and product purity: The addition of suitable achiral additives and cocatalysts,[7] which support the chiral catalyst system, enhance the yield and, surprisingly, in many cases also enhance the enantioselectivity very efficiently.[8] In reality it is much more than an optimization, and the fact that achiral additives can dramatically change the enantiomeric excess of the products makes the subject so exciting.

In the following, this concept will be illustrated with several very promising recent examples, hopefully highlighting its usefulness for obtaining enantiomerically pure compounds. Naturally, additives not only help to optimize a reaction by increasing good *ee* values to excellent *ee* values, but can also efficiently improve reactions with low enantioselectivity to modest (good, or even very good) enantioselectivity. This will be shown in this review as well. For methodological research this effect should be important as it can sometimes suddenly pave the way for new catalytic concepts. It should be emphasized here that in most cases (but not all) the improved methodologies may still be far from what would be desired by industrial chemists and may not fulfill the prerequisites for

[*] Prof. Dr. M. Shibasaki, Dr. E. M. Vogl, Dr. H. Gröger[+]
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: mshibasa@mol.f.u-tokyo.ac.jp

[+] Present address:
SKW Trostberg AG
Special and Fine Chemicals
Department of Research and Development
P.O. Box 1262, D-83303 Trostberg (Germany)

  1433-7851/99/3811-1571 $ 17.50+.50/0

technically feasible catalytic processes. But this is hopefully just a matter of time.

2. Mechanistic Considerations

The improvement of a catalytic enantioselective reaction may sometimes appear to be modern alchemy. Naturally, a priori predictions of which from a variety of additives may be beneficial are hard to make. However, it is also hard to explain why an additive is beneficial (at least in many cases). Although a confusing variety of reasons and several mechanistic effects which influence the catalysis are likely to exist and due to the complexity of the resulting catalytic systems, which make reproducible results difficult to obtain, the role of additives can only be elucidated after mechanistic studies. Until now such mechanistic studies have been carried out in only a few cases. Therefore, only general reasons (usually vaguely stated in the original papers) for how additives can function may be outlined here.

a) Probably one of the most common effects of additives is to deoligomerize nonactive (or less active) catalyst structures, resulting in the formation of the desired active monomeric catalyst species (or analogous di- and trimeric catalyst species).[9] The homogenization of a heterogeneous catalytic system through the addition of suitable donors therefore represents a way to increase the number of active sites.

b) Bases are also often considered to enable a faster dissociation of the formed catalyst–product complex by ligand exchange reactions.[10] In that way the active catalyst is regenerated more rapidly and the activity is increased, which can often result in higher *ee* values as the reaction can then be carried out at lower temperature.

c) In particular basic additives may be able to coordinate to the metal center permanently or temporarily, thereby changing the geometry of the catalyst in a favorable way. This may accelerate the desired reaction by turning the catalyst into a more active species,[11] or increase the *ee* value owing to a different chiral geometry around the active center. In addition this may be one of the more predictable effects of additives, as molecular modeling might be employed to understand the resulting geometry.

d) Through tuning of the ligand sphere or the electronic properties of the environment of the catalyst, the mechanistic pathway of the reaction may also be changed completely. Accordingly, the presence of halides as counterions can lead to a more efficient (neutral) pathway in a palladium-catalyzed reaction (see Scheme 10).

e) Additives might also serve as a "buffer", for example, to maintain the water concentration at a defined level. Therefore, molecular sieves are sometimes applied even in combination with water to keep the moisture of a reaction at an optimized level.[12] Other effects of molecular sieves can also be postulated (surface-assisted desorption of the products, alkali metal exchange[13]).

f) Another additive effect should be mentioned which perhaps represents a challenge as it might also be utilized deliberately: the design of a catalyst poison for an undesired

Erasmus M. Vogl, born in 1970 in Schwabach (Germany), received a M.Phil. from the University of Cambridge (UK) in 1994, a Diplom from the Universität Düsseldorf in 1995, and a Ph.D. from the Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr, in 1997. He was a Visiting Fellow at the Jawaharlar Nehru Center, Bangalore (1996) and a Postdoctoral Fellow at the University of Tokyo (1997–1998), and joined Bayer AG, Leverkusen in 1999, where he is working on a project in Boston.

E. M. Vogl

H. Gröger

M. Shibasaki

Harald Gröger, born in 1968 in Erlangen (Germany), studied chemistry at the Universität Erlangen and the Universität Oldenburg, where he received his Ph.D. under the direction of Professor Jürgen Martens. He was a Postdoctoral Fellow at the University of Tokyo (1997–1998), and joined the Chemical Research division of SKW Trostberg AG in 1998. He is currently involved in the development of chiral building blocks.

Masakatsu Shibasaki, born in 1947 in Saitama (Japan), received his Ph.D. from the University of Tokyo under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University. In 1977 he joined Teikyo University as an associate professor, became a group leader at Sagami Chemical Research Center in 1983, and a professor at Hokkaido University in 1986. Since 1991 he has been a Professor at the University of Tokyo. He has received a number of distinctions including the Fluka Prize in 1996, the Elsevier Award in 1998, and the Pharmaceutical Society of Japan Award in 1999. This year he will deliver the George Büchi Lecture at the Massachusetts Institute of Technology, the Syntex Distinguished Lecture at Colorado State University, and the Brystol-Myers Squibb Lecture at Harvard University.

catalyst species. That is, upon treatment of a mixture of transition metal complexes with an additive, the complex which shows an undesired (nonenantioselective) catalytic activity, reacts highly selectively with the additive, resulting in the formation of an "inert" transition metal complex without any catalytic activity. The catalytic activity of the desired catalytic species, however, should not be influenced by these additives.

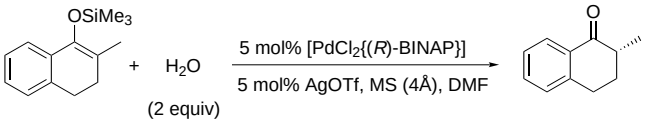
When trying to explain various additive effects, one should be well aware that our understanding is as yet rudimentary. The need for an automated screening process or even a combinatorial screening of additives should (if practically possible) also be considered. On the other hand, it would be desirable to obtain detailed mechanistic understanding of the role of additives.

3. Additives in Asymmetric Catalysis

3.1. Amines and Pyridines

Generally, nitrogen bases are the most common additives,[14] and it has become usual practice to screen nitrogen bases (amongst other additives) to improve catalytic asymmetric processes. For the enantioselective hydrogenation of simple ketones catalyzed by a new Rh–diphosphane complex, such screening was carried out with careful variation of the Rh/additive ratio.[15] For acetophenone as substrate the yield could be increased from 45 to 97% and the enantiomeric excess from 57 to 95% *ee* when 0.3 catalyst equivalents of 2,6-lutidine were added.

Also impressive is the finding by Nakai et al. that addition of a small amount of amine in a Pd-catalyzed protonation reaction to form chiral α-substituted carbonyl compounds gives improved results.[16] In the absence of base only poorly reproducible yields and largely varying enantioselectivities have been obtained. In contrast, after addition of base the desired high yields and good enantioselectivities could always be reproduced (Scheme 1). Interestingly the positive effect of

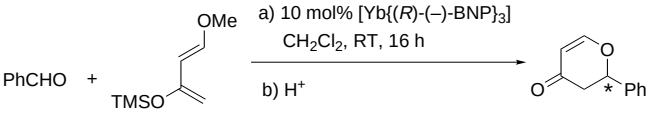


no additive (RT - 30 °C, 84 - 5 h): 25 - 85% yield, 44 - 73% *ee*
0.5 mol% *i*Pr$_2$NH (50 °C, 18 h): 83% yield, 79% *ee*

Scheme 1. Protonation of silyl enol ethers.[16] BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; Tf = F_3CSO_2.

the additive was attributed to a quite unexpected scenario. Instead of activating the catalyst, the added diisopropylamine was causing a (desired) catalyst poisoning! The additive deactivates only the catalytic species that catalyzes the reaction with low or no enantioselection without altering the catalytic activity of the "surviving" desired Pd species much. This ensures that the reaction proceeds in high yields (83%) and with good enantioselectivity (79% *ee*).

Also for an asymmetric hetero-Diels–Alder reaction, catalyzed by a chiral Yb^{III}–phosphate complex, the addition of a base (here 2,6-lutidine) caused a jump from 70 to 89% *ee* at room temperature (Scheme 2; BNP = 1,1′-binaphthyl-2,2′-



no additive: 77% yield, 70% *ee*
10 mol% 2,6-lutidine : 94% yield, 89% *ee*

Scheme 2. Hetero-Diels–Alder reaction.[17] TMS = Me_3Si.

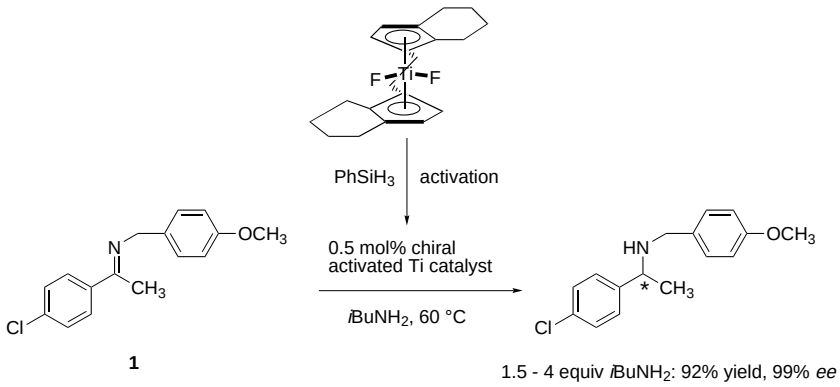
diyl phosphate).[17] Since the reaction without an additive proceeds under heterogeneous conditions, and since the addition of bases increases the solubility of the catalyst in dichloromethane (catalyst solutions without precipitate are of advantage and generally seem to work better), the addition of basic ligands like hexamethyl phosphoramide (HMPA) has also been reported. However, in this case the reaction was seriously retarded, an effect we also observed for other systems. It is likely that when strongly coordinating additives are provided, the catalyst is easily deactivated or the catalyst structure collapses.

The asymmetric synthesis of chiral amines from imines is industrially important. An interesting additive effect has been observed recently by Buchwald et al., when investigating the asymmetric hydrosilylation of imines.[18] Despite high TON and enantioselectivities, previous efficient hydrosilylation methods have been limited to imines that are not sterically hindered.[19] This limitation has now been overcome by Buchwald et al. simply by adding an achiral base to the reaction mixture. Thus, in the presence of 0.05–1 mol% of a chiral titanium catalyst and isobutylamine (or *sec*-butylamine) as an additive, excellent enantioselectivities in the range of 91–99% *ee* and enhanced yields of 86–97% were obtained with a variety of sterically hindered substrates such as **1** (Scheme 3).

The importance of the additive can be recognized by looking at the model reaction with *N*-benzyl-1-indanimine. The authors found that the absence of an additive led to a conversion of only 5%, whereas 100% conversion and 92% *ee* were achieved with isobutylamine as a base. Furthermore, in contrast to previous methods the high enantiomeric excesses do not depend on the *E*/*Z* ratios of the imines. Although the mechanistic course has not been clarified in detail, the added achiral amine appears to cleave the complex between the titanium catalyst and the chiral amino product. A representative example for the highly efficient asymmetric Buchwald hydrosilylation, in which an enantiomeric excess of 99% was obtained, is shown in Scheme 3.

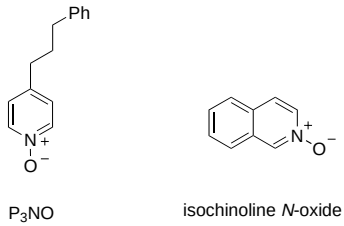
3.2. Pyridine *N*-Oxides

Solutions for industrial applications of chiral catalysis, here the manganese salen catalyzed asymmetric epoxidation of olefins, were recently reported by teams from Merck & Co.,



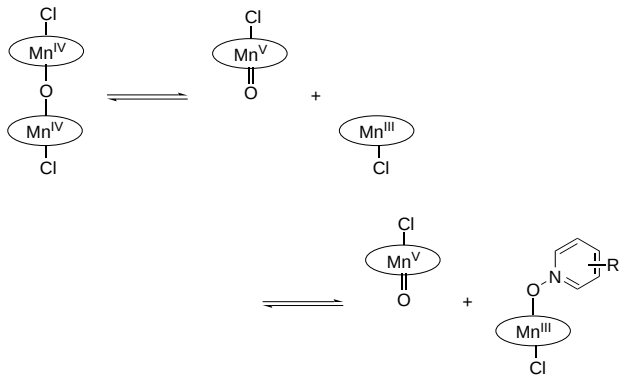
Scheme 3. Hydrosilylation of imines.[18]

Inc.[20] and SmithKline Beecham Pharmaceuticals.[21] Both groups utilized pyridine *N*-oxide derivatives as additives; the oxidant was aqueous sodium hypochlorite. By screening several pyridine *N*-oxides, the Merck group found that for the chiral manganese salen catalyzed epoxidation of indene the addition of 4-(3-phenylpropyl)pyridine *N*-oxide (P_3NO, Scheme 4) gives the best results. The indene oxide product obtained is a chiral building block of the HIV protease inhibitor Indinavir.



Scheme 4.

In the case of a salen complex catalyzed enantioselective epoxidation to afford chiral 2,2-dimethyl-6-pentafluoroethylchromene oxide, the addition of isochinoline *N*-oxide allowed a decrease in catalyst loadings to a remarkable 0.1–0.4 mol%. In fact, the positive effect of the addition of pyridine *N*-oxide derivatives on enantioselectivity had been noted earlier.[22] It was proposed that the effect of *N*-oxide additives could be due to the set of equilibria shown in Scheme 5.[23] The active (salen)Mn^V=O complex is thought to



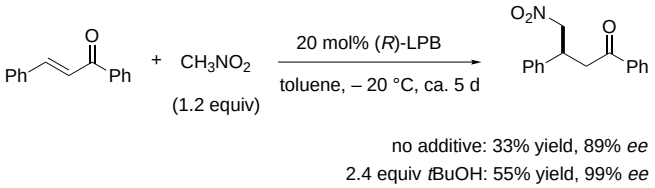
Scheme 5. Proposed role of pyridine *N*-oxides in manganese-catalyzed epoxidations.[23]

undergo a reversible coupling with a Mn^{III} complex to generate an inactive μ-oxo dimer. Through additive binding of the pyridine *N*-oxide derivative to the coordinatively unsaturated Mn^{III} complex, the equilibrium is shifted towards the Mn^V oxo intermediate. Owing to the increased concentration of the active Mn^V oxo species a rate acceleration of the epoxidation is then expected.

Very recently Komatsu et al. used pyridine *N*-oxide as an additive for the asymmetric aziridination of styrene derivatives by transfer of a nitrogen atom from a chiral nitridomanganese complex.[24] However, this reaction is not a catalytic process (yet).

3.3. Alcohols

Even simple alcohols like *tert*-butyl alcohol have successfully been used as additives, and pronounced and surprising ligand effects could be observed.[25] The asymmetric Michael addition of nitromethane to chalcone, catalyzed by a chiral lanthanum–potassium–BINOL complex (LPB complex; BINOL = 1,1′-binaphthol), proceeded in 33% yield and with 89% *ee*. After addition of 2.4 molar equivalents of *tert*-butyl alcohol (that is, 12 equivalents based on the catalyst), the yield increased to 55% and the enantiomeric excess reached 99% *ee* (Scheme 6). Here the exact amount of additive did

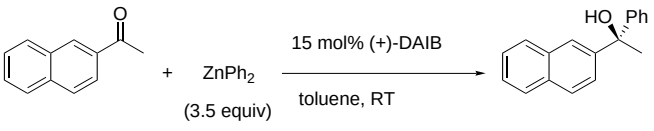


Scheme 6. Michael addition of nitromethane to enones.[25]

not have a pronounced effect on the yield and enantiomeric excess (use of 20–480 mol% of additive gave comparable results). Similar improvements, using *tert*-butyl alcohol as an additive, were obtained with the substrate 4-chlorochalcone, suggesting that the effect may be general.

Also in the case of an asymmetric Heck reaction, the yields and *ee* values were surprisingly improved when *tert*-butyl alcohol was added.[26] In terms of mechanism it was suggested that the additive might prevent a specific substrate–palladium interaction which produces oxidation side products.

It has also been reported that even when organometallic reagents are used, an additive like methanol, with an acidic proton, can have positive effects. Dosa and Fu investigated the catalytic asymmetric addition of $ZnPh_2$ to ketones, the chiral information being provided by an amino alcohol (3-*exo*-(dimethylamino)isoborneol, DAIB; Scheme 7).[27] Although a promising level of enantioselectivity was observed in the



no additive: 26% yield, 64% *ee*
1.5 equiv MeOH: 58% yield, 72% *ee*

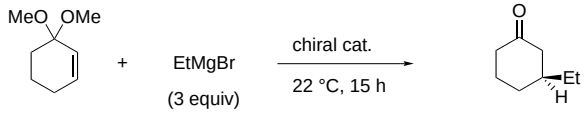
Scheme 7. Addition of $ZnPh_2$ to ketones.[27]

absence of an additive (64% *ee*), the yield of the product was low (26%). In the presence of 1.5 equivalents of methanol the yield increased to 58% and the *ee* value reached 72% for the substrate shown in Scheme 7. For other substrates *ee* values up to 91% could be obtained in the presence of methanol, which was added to the DAIB/$ZnPh_2$/toluene mixture before the reaction, and may alter the nature of the zinc species in solution. As frequently seen when metal alkoxides are incorporated in the catalyst structure, there was a nonlinear relationship between the *ee* values of product and catalyst.

3.4. P-Based Additives

3.4.1. Phosphanes

Surprisingly, there seems to be little limitation for beneficial effects of additives in terms of the type of reaction. A systematic investigation, this time of the influence of various achiral phosphane additives on the enantioselectivity of a Ni-catalyzed asymmetric addition of Grignard reagents to unsaturated cyclic acetals (Scheme 8), was reported by



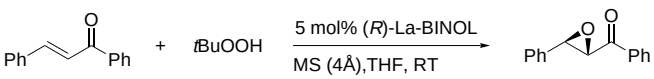
5 mol% [(*S*,*S*)-(chiraphos)$NiCl_2$]: 80% yield, 10% *ee*
5 mol% [$(PPh_3)_2NiCl_2$], 5 mol% (*S*,*S*)-chiraphos: 90% yield, 85% *ee*

Scheme 8. Addition of Grignard reagents to unsaturated cyclic acetals.[28]

Hoveyda et al.[28] Trying to avoid a "background reaction" arising from the action of an achiral catalyst, the authors first isolated (prior to use) the catalytically active (*S*,*S*)-(chiraphos)$NiCl_2$ complex prepared from [$(PPh_3)_2NiCl_2$] and (*S*,*S*)-chiraphos (chiraphos = 2,3-bis(diphenylphosphanyl)butane). However, later it was observed that in some cases the catalyst prepared in situ actually provided superior selectivity (see Scheme 8) due to the additional achiral phosphane ligands present in the mixture. Product *ee* values from lower than 5 up to 82% were then obtained for a test reaction when different phosphanes were added to the (*S*,*S*)-(chiraphos)$NiCl_2$ catalyst.

3.4.2. Phosphane Oxides

A pronounced ligand effect on the enantioselectivity in the chiral lanthanum complex catalyzed asymmetric epoxidation of enones was found by Inanaga and co-workers (Scheme 9).[29] In the reaction of chalcone, simply addition of



no additive (3 h): 86% yield, 73% *ee*
15 mol% $Ph_3P{=}O$ (0.5 h): 99% yield, 96% *ee*

Scheme 9. Epoxidation of enones.[29]

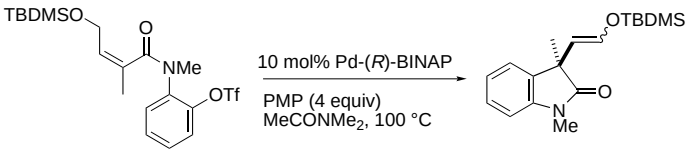
triphenylphosphane oxide led to an increase in the *ee* value of the epoxide products from 73% (no additive) to 96% with simultaneous improvement of the yield from 86 to 99%. It is perhaps interesting to point out the subtleness of the process by considering the precise nature of the additive. Whereas similarly good results have been obtained upon addition of tri-*p*-tolylphosphane oxide (95% yield and 94% *ee* after 1 h), with tri-*o*-tolylphosphane oxide the *ee* value dropped back to 73% (96% yield). With *n*-butylphosphane oxide as an additive the results have been virtually the same as without an additive (88% yield and 73% *ee*). The method was also found to be quite general for other enones. To rationalize the beneficial effect of Ph_3PO, it has been suggested that the additive might prevent an oligomerization of the catalyst (the metal precursor was added to a mixture of phosphane oxide and ligand), or it might depolymerize the catalyst after formation. The amount of molecular sieves (MS) was also found to have a strong influence on the *ee* value. Future experiments should prove important for clarifying how even molecular sieves can influence the *ee* value. To be able to carry out practical optimizations of catalytic processes, it would be necessary to know if, for example, owing to kinetic advantages a dissociation of the products is assisted or if molecular sieves perhaps just control the exact amount of water.[30]

The addition of phosphane oxide was also very effective in the cyanosilylation of aldehydes utilizing a new Lewis base/Lewis acid catalyst (with general applicability to aromatic, aliphatic, and α,β-unsaturated aldehydes), and very high *ee* values have been obtained.[31] In fact initially the *ee* values were below 10%, but after the addition of phosphane oxide and with very slow addition of the substrate (syringe pump) it was possible to obtain the products with up to 98% *ee* and even in improved yields.

3.5. Ionic Additives

3.5.1. Halides

A clear picture of the effect of salt additives, like tetrabutylammonium halides, was recently drawn by Overman and Poon for the asymmetric Heck reaction.[32] The cyclization of the (*Z*)-butenanilide triflate **2** with Pd–(*R*)-BINAP leads to (*R*)-oxindole **3** with 43% *ee* (Scheme 10). However, after addition of only one molar equivalent of tetrabutylammonium bromide, product **3** was obtained with a creditable 93% *ee*. In the presence of such a halide additive, the crucial insertion step of the reaction is diverted to a neutral pathway via a neutral intermediate. (Contrary to this, a cationic pathway is generally assumed to be favored in the presence of silver salts.) In the case of substrate **2**, the neutral



2 **3**

no additive: 72% yield, 43% *ee*
1 equiv nBu_4NBr: 59% yield, 93% *ee*

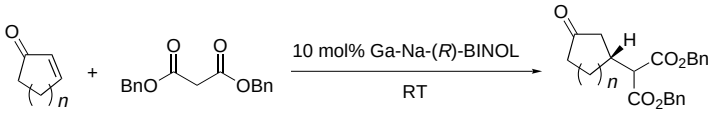
Scheme 10. Heck reaction.[32] PMP = 1,2,2,6,6-pentamethylpiperidine; TBDMS = $tBuMe_2Si$.

pathway seems to proceed with a much higher degree of stereoinduction than the cationic pathway, therefore yielding the product with high *ee* values. Such improved distinction between two competing pathways with a different degree of stereoselection seems to be one of the more common reasons why achiral additives can be so effective.

In a previous paper Ashimori and Overman showed that both enantiomers of a spirooxindole similar to **3** could be synthesized, although the same chiral information ((*R*)-BINAP) was used. Depending only on the additives, the *ee* value obtained changed from 71 % with Ag_3PO_4 to 66 % of the opposite enantiomer when 1,2,2,6,6-pentamethylpiperidine was present.[33]

3.5.2. NaOR/BuLi

Heterobimetallic complexes have been reported to self-assemble with additional (catalytic) amounts of NaO*t*Bu or BuLi to provide catalysts of improved efficiency.[34] Results of the enhancement of the efficiency for an asymmetric Michael reaction utilizing a Ga-Na-(*R*)-BINOL complex are depicted in Scheme 11. When sodium dibenzyl malonate (9 mol %) was added instead of NaO*t*Bu, the same effect could be obtained.



n = 1: no additive (72 h): 32% yield, 89% *ee*
9 mol% NaO*t*Bu (22 h): 96% yield, 98% *ee*

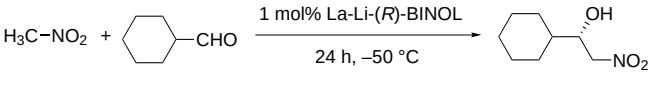
n = 2: no additive (143 h): 45% yield, 98% *ee*
9 mol% NaO*t*Bu (21 h): 87% yield, 98% *ee*

n = 3: no additive (73 h): trace amount of product
9 mol% NaO*t*Bu (73 h): 79% yield, >99% *ee*

Scheme 11. Michael reaction.[34]

By using a similar activation strategy, catalytic asymmetric nitroaldol reactions could also be improved considerably (Scheme 12). It was proposed that by combined addition of water and BuLi a LiOH species is generated that is incorporated into the structure of La-Li-BINOL.

Noyori et al. demonstrated previously that the addition of KO*t*Bu or KOH in combination with diamine ligands is very beneficial for the enantioselective hydrogenation of aromatic



no additive : 6% yield, 88% *ee*
1 mol% H_2O, 0.9 mol% BuLi: 73% yield, 89% *ee*

Scheme 12. Nitroaldol reaction.[34]

ketones. Very excellent yields and *ee* values have been reported utilizing the BINAP – Ru^{II} catalyst system.[35]

Since, for example, BuLi as an additive is very reactive, it may not be applicable for too many other systems. It may, however, be suggested that the addition of quite reactive species to a catalyst mixture might in general still be interesting initially, as they may be transformed into truly beneficial additives in situ (BuLi to LiOH).

3.5.3. Acetic Acid and Halides

A new catalyst system currently applied technically for homogeneous enantioselective hydrogenation was recently developed by a research team of Ciba-Geigy.[36] Acetic acid and iodide (added as Bu_4NI) were found to be crucial additives. For the enantioselective synthesis of a number of important acyl anilide pesticides—the most important example being the herbicide metolachlor[37]—an asymmetric hydrogenation of *N*-arylimines can be utilized. However, the activity of existing chiral catalytic systems had been far too low. The use of a new class of iridium ferrocenyl diphosphane complexes, which turned out to be very stable under reaction conditions, gave very active and productive catalysts. However, the breakthrough on the way to a production process of metolachlor came only with the addition of both acetic acid and iodide. Ligand optimization showed that $[(Ir(cod)Cl]_2$/xyliphos[38] (cod = 1,5-cyclooctadiene, xyliphos = (*R*)-1-[(*S*)-2-(diphenylphosphanyl)ferrocenyl]ethyldi(3,5-dimethylphenyl)-phosphane) was the optimal catalyst, and under a hydrogen pressure of 80 bar and with a remarkable substrate/catalyst ratio of 750000 – 1000000 complete conversion could be reached within three to four hours at 50 °C. The optical yields have only been moderate (78 % *ee*), but the TOF was excellent (350000 h^{-1}). It is difficult to explain why iodide and acid have such a remarkable (synergetic) effect. Until now, the mechanism responsible could not be clarified in detail.

4. Summary and Outlook

A number of very recent examples of how addition of, for example, nitrogen bases, alcohols, phosphanes, phosphane oxides, pyridine *N*-oxides, halides, or acid can positively effect asymmetric catalytic reaction systems was discussed. In our approach we deliberately covered all sorts of organic reactions, knowing that each case may be different and mechanistic similarities may not exist even for the same additive.

Only weakly coordinating ligands (for example, phosphane oxides or pyridine *N*-oxides) could perhaps be seen among the most promising additives. In some cases such ligands might

temporarily occupy the empty reactive sites of catalyst complexes while the catalyst is "at rest". This could perhaps be developed to effect a general catalyst protection or stabilization.[39]

To date, in many instances additives have been found by chance rather than by logical prediction. We imagine that the recent developments and reaction systems selected could provide a pool of ideas for optimizing industrial processes, as well as being of practical value for similar research on asymmetric reactions in general.[40] Clearly the most urgent goal of academic research in asymmetric catalysis is to rationally reduce the amount of catalyst—and additives may play a crucial role in this process.

E.M.V. and H.G. thank the Japanese Society for the Promotion of Science (JSPS) and the Japan Science and Technology Corporation (JST), respectively, for postdoctoral fellowships.

Received: November 27, 1998 [A 321 IE]
German version: *Angew. Chem.* **1999**, *111*, 1671 – 1680

[1] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.
[2] a) R. Noyori, *Chem. Soc. Rev.* **1989**, *18*, 187 – 208; b) R. Noyori, *Science* **1990**, *248*, 1194 – 1199; c) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 629 – 631.
[3] a) S. Akutagawa in *Organic Synthesis in Japan: Past, Present, and Future* (Eds.: R. Noyori, T. Hiraoka, K. Mori, S. Murahashi, T. Onoda, K. Suzuki, O. Yonemitsu), Tokyo Kagaku Dozin, Tokyo, **1992**, p. 75; b) S. Inoue, H. Takaya, K. Tani, S. Otsuka, T. Sato, R. Noyori, *J. Am. Chem. Soc.* **1990**, *112*, 4897 – 4905.
[4] a) T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1977**, 2599 – 2602; b) T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1982**, *23*, 685 – 688.
[5] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974 – 5976; b) E. N. Jacobsen in *Comprehensive Organometallic Chemistry II, Vol. 12* (Eds.: E. W. Abel, F. G. Stone, E. Wilkinson), Pergamon, New York, **1995**, p. 1097.
[6] H.-U. Blaser, B. Pugin, F. Spindler in *Applied Homogeneous Catalysis with Organometallic Compounds*, *Vol. 2* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, p. 994.
[7] a) For example, KOH/amines are used to control the distribution of side products in hydroformylation reactions: C. D. Frohnung, C. W. Kohlpaintner in *Applied Homogeneous Catalysis with Organometallic Compounds*, *Vol. 2* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, p. 74. b) Additives used for the hydrodimerization of butadiene may be another example: N. Yoshimura in *Applied Homogeneous Catalysis with Organometallic Compounds*, *Vol. 2* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, p. 351. c) Strictly speaking only species added in catalytic amounts may be considered to be "true" additives, otherwise (> 1 mol equiv) they may just be regarded as part of a special solvent mixture.
[8] Of course, the chiral ligand itself may already accelerate the catalytic reaction (ligand-accelerated catalysis, LAC): D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159 – 1171; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059 – 1070.
[9] The importance of the degree of association of the catalyst can be illustrated by considering that the concentration of the reaction is crucial in some instances: a) G. E. Keck, D. Krishnamurthy, *J. Am. Chem. Soc.* **1995**, *117*, 2363 – 2364; b) Y. Jiang, L. Gong, X. Feng, W. Hu, W. Pan, Z. Li, A. Mi, *Tetrahedron* **1997**, *42*, 14327 – 14338.
[10] See, for example, M. Nakajima, M. Saito, M. Shiro, S.-I. Hashimoto, *J. Am. Chem. Soc.* **1998**, *120*, 6419 – 6420.
[11] See, for example, S. Casolari, P. G. Cozzi, R. Orioli, E. Tagliavini, A. Umani-Ronchi, *Chem. Commun.* **1997**, 2123 – 2124.
[12] For a study on the role of molecular sieves, see M. Terada, Y. Matsumoto, Y. Nakamura, K. Mikami, *Chem. Commun.* **1997**, 281 – 282.
[13] a) T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783 – 4784; b) Y. Koga, M. Sodeoka, M. Shibasaki, *Tetrahedron Lett.* **1994**, *35*, 1227 – 1230.
[14] Various other examples exist where nitrogen bases have a strong influence on the selectivity of the reaction; see for example a) S. Kobayashi, M. Kawamura, *J. Am. Chem. Soc.* **1998**, *120*, 5840 – 5841; b) D. A. Evans, S. G. Nelson, *J. Am. Chem. Soc.* **1997**, *119*, 6452 – 6453.
[15] Q. Jiang, Y. Jiang, D. Xiao, P. Cao, X. Zhang, *Angew. Chem.* **1998**, *110*, 1203 – 1207; *Angew. Chem. Int. Ed.* **1998**, *37*, 1100 – 1103.
[16] M. Sugiura, T. Nakai, *Angew. Chem.* **1997**, *109*, 2462 – 2464; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2366 – 2368.
[17] a) T. Hanamoto, H. Furuno, Y. Sugimoto, J. Inanaga, *Synlett* **1997**, 79 – 80. b) For a fundamental contribution on nitrogen base additives that describes a synthesis of both enantiomers of a product using a single chiral source and added achiral ligands, see S. Kobayashi, H. Ishitani, *J. Am. Chem. Soc.* **1994**, *116*, 4083 – 4084.
[18] X. Verdaguer, U. E. W. Lange, S. L. Buchwald, *Angew. Chem.* **1998**, *110*, 1174 – 1177; *Angew. Chem. Int. Ed.* **1998**, *37*, 1103 – 1107.
[19] X. Verdaguer, U. E. W. Lange, M. T. Reding, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 6784 – 6785.
[20] C. H. Senanayake, G. B. Smith, K. M. Ryan, L. E. Fredenburgh, J. Liu, F. E. Roberts, D. L. Hughes, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Tetrahedron Lett.* **1996**, *37*, 3371 – 3274.
[21] D. Bell, M. R. Davies, F. J. L. Finney, G. R. Green, P. M. Kincey, I. S. Mann, *Tetrahedron Lett.* **1996**, *37*, 3895 – 3898.
[22] a) R. Irie, Y. Ito, T. Katsuki, *Synlett* **1991**, 265 – 266; b) B. D. Brandes, E. N. Jacobsen, *J. Org. Chem.* **1994**, *59*, 4378 – 4380.
[23] E. N. Jacobsen, L. Deng, Y. Furukawa, L. E. Martinez, *Tetrahedron* **1994**, *50*, 4323 – 4334.
[24] S. Minakata, T. Ando, M. Nishimura, I. Ryu, M. Komatsu, *Angew. Chem.* **1998**, *110*, 3596 – 3598; *Angew. Chem. Int. Ed.* **1998**, *37*, 3392 – 3394.
[25] K. Funabashi, Y. Saida, M. Kanai, T. Arai, H. Sasai, M. Shibasaki, *Tetrahedron Lett.* **1998**, *39*, 7557 – 7558.
[26] K. Kondo, M. Sodeoka, M. Mori, M. Shibasaki, *Synthesis* **1993**, 920 – 930.
[27] P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445 – 446.
[28] E. Gomez-Bengoa, N. M. Heron, M. T. Didiuk, C. A. Luchaco, A. H. Hoveyda, *J. Am. Chem. Soc.* **1998**, *120*, 7649 – 7650.
[29] a) K. Daikai, M. Kamaura, J. Inanaga, *Tetrahedron Lett.* **1998**, *39*, 7321 – 7322; b) M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 2329 – 2330.
[30] a) S. Watanabe, Y. Kobayashi, T. Arai, H. Sasai, M. Bougauchi, M. Shibasaki, *Tetrahedron Lett.* **1998**, *39*, 7353 – 7356.
[31] Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.*, in press.
[32] L. E. Overman, D. J. Poon, *Angew. Chem.* **1997**, *109*, 536 – 538; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 518 – 521.
[33] A. Ashimori, L. E. Overman, *J. Org. Chem.* **1992**, *57*, 4571 – 4572.
[34] T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai, M. Shibasaki, *Chem. Eur. J.* **1996**, *2*, 1368 – 1372.
[35] T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2675 – 2676.
[36] a) F. Spindler, B. Pugin, H.-P. Jalett, H.-P. Buser, U. Pittelkow, H.-U. Blaser, *Chem. Ind.* (Dekker) **1996**, *68*, 153 – 166; b) F. Spindler, H.-U. Blaser in *Transition Metal for Organic Synthesis* (Eds.: M. Beller, C. Bolm), WILEY-VCH, Weinheim, **1998**, chap. 1.1.4.
[37] G. M. Ramos Tombo, D. Bellus, *Angew. Chem.* **1991**, *103*, 1219 – 1241; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1193 – 1215.
[38] Such ferrocenyldiphosphane ligands may perhaps be particularly susceptible to additives due to their complex structure with respect to the metal center.
[39] Of course, amines in general might still be the most important additives in the future.
[40] Yu et al. utilize another interesting additive (iPrSBEt$_2$), or in this case perhaps only an additional achiral reagent, for example, for catalytic asymmetric allenylations: G.-M. Yu, S. K. Yoon, K. Baek, J.-Y. Lee, *Angew. Chem.* **1998**, *110*, 2504 – 2506; *Angew. Chem. Int. Ed.* **1998**, *37*, 2392 – 2395.