High-Throughput and Parallel Screening Methods in Asymmetric Hydrogenation

Christoph Jäkel and Rocco Paciello*

BASF Aktiengesellschaft, Basic Chemicals Research, GCB - M 313, 67098 Ludwigshafen, Germany

Received December 7, 2005

Contents

1. Introduction

High-throughput and parallel screening methods are being used more and more extensively in various areas of chemistry, including enantioselective synthesis.[1] This due to the extremely small energy differences determining such critical factors as enantioselectivity. Yue and Nugent[2] (Scheme 1) and Boulton et al.[3] (Scheme 2) recently described two examples, which illustrate this quite well.

In both cases, completely unexpected solutions were identified for the problems studied. A conformationally flexible ligand, 2,4-bis(diphenylphosphino)pentane **3**, was found to be optimal in the enantioselective hydrogenation of 3-alkylidenlactams.[2] Phanephos **10** was found to be optimal in the hydrogenation of an (*E*)-4,4-diaryl-3-butenoate ammonium salt **8**. This ligand had shown lower enantioselectivities in comparison to phospholane-type ligands in earlier hydrogenation studies within this group.[3]

In recent years, industrial applications of asymmetric hydrogenation[4] have increased considerably and many examples have been summarized in the literature.[5]

Information, however, on catalyst identification procedures, route selection, and scale-up is usually scattered and sometimes not easily available. We have been especially interested in understanding which strategies are used for route selection and which for optimization and scale-up and why (availability of equipment, sensitivities, reproducibility, size of parameter space that can be tested, etc). We will focus this review on these issues. We will also primarily focus on work done in the last 2−3 years, because this has been a particularly fruitful time in this area of research.

Due to the historical development of this field, many descriptions of this type of work can be found using keywords such as "combinatorial chemistry" or "high-throughput screening". A more detailed analysis, however, shows that work done in such areas as enantioselective hydrogenation, an area of particular interest in industrial as well as academic laboratories, does not actually fit well in the original definitions of these terms. For example, due to the nature of the chemistry involved in this area, high-throughput often involves relatively modest numbers of reactions, in comparison to some of the biological screening methods described in the literature. A large amount of work has been done, as shown in the examples above, using only a relatively limited number of parallel reactors.

In this review, we wish to discuss such strategies using the example of enantioselective hydrogenation. We wish to order them according to the stages of process development, which have been discussed in more general terms for fine chemical synthesis a number of times in the literature,[6] and to analyze their strengths and weaknesses based on the needs of the different stages.

The methodologies of interest to us focus on route selection and the first stages of scale-up. Constraints to be considered included raw material costs, time pressure, and the necessity for using existing equipment. Raw material costs, such as ligand costs in enantioselective synthesis, can be a significant factor in the decision to commercialize or not. The time available for identifying and developing a route for chiral intermediates has become considerably shorter in the last years, as pharmaceutical companies attempt to reduce their own development times. The fact that many optically

* To whom correspondence should be addressed. Tel: +49 621 60-78181. Fax: +49 621 66-78181. E-mail: rocco.paciello@basf.com.

10.1021/cr040675a CCC: $59.00
Published on Web 06/30/2006 PAGE EST: 30.1

Christoph Jäkel was born in 1971 in Unkel/Germany. He received his Ph.D. degree in 2001 from the University of Bonn under the supervision of Prof. K. H. Dötz. In 2002, he entered the Basic Chemicals Research department of BASF after postdoctoral work with Prof. B. M. Trost at Stanford University as a Feodor-Lynen-Fellow of the Alexander von Humboldt Foundation. He now heads the new joint catalysis research laboratory of BASF and the University of Heidelberg—CaRLa. His current research interests are focused on the application of homogeneous catalysis toward topics such as the efficient utilization of new raw materials, C–C and C–X bond-making processes, and enantioselective addition reactions of small molecules to olefins.

Rocco Paciello did his undergraduate work at MIT and received his degree in Chemistry in 1982. He did his graduate work at CalTech in the group of Professor John Bercaw and received his Ph.D. in Chemistry in 1987. He was a Humboldt research fellow at the Technical University in Münich in the group of Professor Wolfgang Herrmann until 1989. He started his industrial career at DuPont in Wilmington, Delaware, in 1989 and changed firms in 1992. At that point, he became a research chemist at BASF in Ludwigshafen, Germany. After a short stint as assistant plant manager, he returned to research in 2000. He is presently a senior research manager and leads a group focused on homogeneous catalysis. His research interests cover all aspects of homogeneous catalysis, with an emphasis on catalyst design, synthesis, scale-up of processes, and process technology. Present areas of research encompass the synthesis of organometallic complexes for use as electronic materials, asymmetric synthesis, hydroformylation (both low and high pressure), and processes for making and functionalizing olefins.

active compounds tend to be needed in small quantities makes the use of existing equipment necessary to achieve a reasonable cost structure.

Another way of viewing the development process is to see it as a change from a problem in chemistry (finding the right route) to one of chemical engineering (getting it to work economically at large scale). At the start of the process in route selection, chemistry dominates, and one needs methods for testing large numbers of options quickly. Key criteria are diversity and speed. As scale-up proceeds, one is confronted more and more with problems of process design. These lead to a demand for much more precise knowledge of parameters such as temperature, pressure, and catalyst composition. One needs to understand the kinetics of catalyst activation and deactivation and to quantify the observable macroscopic kinetics of the system under the conditions used.[7] The need to use existing equipment can lead to restrictions in the allowable process parameters (*T*, *P*, etc.), which then can lead to massive changes in the reaction kinetics.

The equipment and methodologies used in screening and scale-up address such problems in different ways. They also tend to be used differently depending on goals of the users involved. A pharmaceutical company interested in route definition or scale-up to low kilogram quantities to prepare material for testing will often approach problems much differently than a chemical company interested in scale-up and the production of technical quantities (tons).

2. Fast Screening Methods: Generation of Catalyst Diversity

The development of massive catalyst screening has been hampered mainly by the fact that ligand synthesis and thus structural ligand variation is often not easy. Accordingly, only a few successful approaches have been described so far. Combinatorial methods similar to those used in biochemistry have been described in a number of recent reviews.[8]

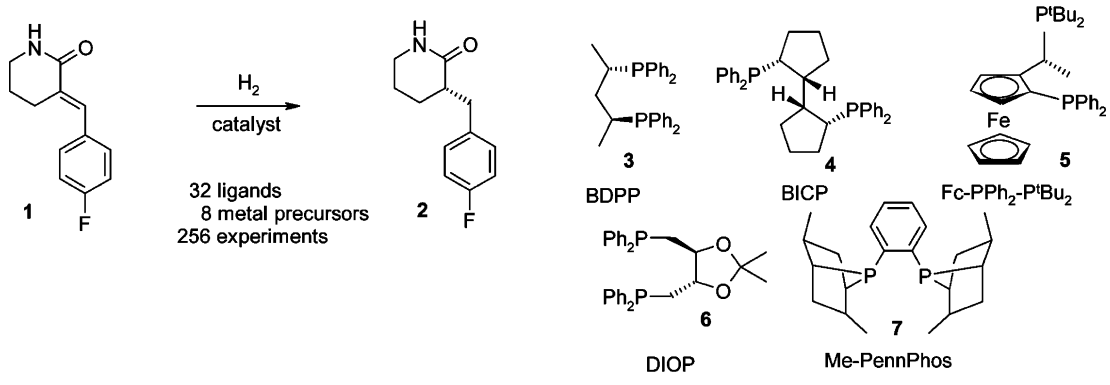
In general, the experience with ligand libraries built up on supports for enantioselective hydrogenations has not been very positive. In most cases, the goal was to generate families of chiral, chelating bisphosphine ligands. This goal has often been achieved. However, the results in catalysis were largely disappointing. This has been due to a number of factors. Among others, the optimization of individual heterogenized systems to achieve activities and selectivities similar to those of homogeneous systems has proven to be a nontrivial problem. Such systems have to be optimized very carefully to achieve high performance. Such optimizations have been carried out successfully. For example, xyliphos was immobilized on silica using a linker.[9] These systems were tested in Ir-catalyzed hydrogenation of the hindered *N*-arylamine precursor leading to (*S*)-metolachlor and yielded extremely high turnover numbers and turnover frequencies. Doing this amount of optimization for every catalyst in a high-throughput study with a large amount of diversity, however, would be very difficult.

Immobilization of monodentate phosphoramidites has also been investigated. The enantioselectivities observed, however, have also not yet achieved useful levels.[10]

Augustine recently described an interesting alternative to heterogenization using linkers.[11] In this work, homogeneous complexes were immobilized on solid supports using heteropolyacids as anchoring agents. This strategy has the enormous advantage that no modification of the chiral ligands is necessary. Extremely high turnover numbers (up to 150 000) were achieved in dimethyl itaconate hydrogenations using ligands such as DuPhos, Skewphos, and BoPhoz. Rhodium losses were very low. The use of such systems in screening is, of course, easily conceivable. However, a study of this sort has not yet to our knowledge been published.

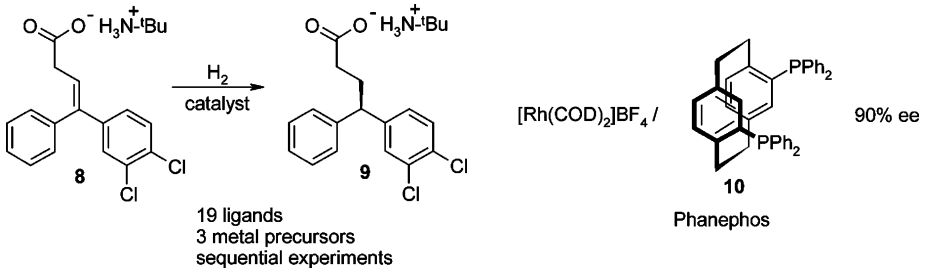
Systems where the ligands have been cleaved from the supports and tested as homogeneous enantioselective hy-

Scheme 1. Screening Results from Ref 2



metal precursor	diphosphine	conversion (%)	ee (%)
$[(COD)_2Ir]BF_4$	**BDPP**	**100**	**91**
$(COD)Ru(methallyl)_2$ + 2HBr	BICP	30	85
$(COD)Ru(methallyl)_2$ + 2HBr	Fc-PPh_2-P^tBu_2	98	70
$(COD)Ru(methallyl)_2$ + BF_3/HBF_4	Pennphos	100	70
$[(COD)_2Ir]BF_4$	BDPP	100	69
$[(COD)_2Ir]BF_4$	DIOP	85	66

Scheme 2. Surprising Finding for the Selective Hydrogenation of a Sertraline Precursor



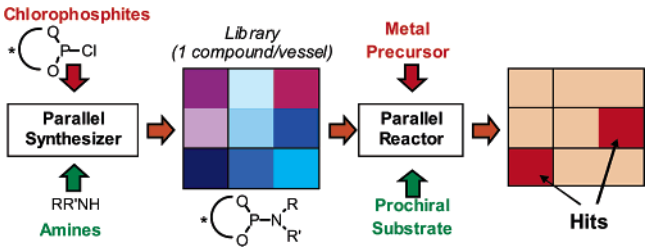
drogenation catalysts have often suffered under the structural limitations inherent to the linker and cleavage strategies used.

Gilbertson, for example, introduced helical peptides containing phosphine side chains to allow coordination of rhodium. In his initial study, he evaluated a library containing 63 different peptides having phosphine groups separated by two or three amino acids.[12] However, only 18% ee was achieved in the asymmetric hydrogenation of the standard substrate methyl 2-acetamidoacrylate. A second-generation library developed on the basis of the first one led to ligands with up to 38% ee.[13] The libraries were synthesized in a 96-pin format using solid-phase chemistry employing the FMOC strategy, and catalyst preparations as well as hydrogenation experiments were executed on the crowns. Comparison with experiments under homogeneous conditions showed comparable results in water, but low and even inverted enantioselectivities in tetrahydrofuran or dichloromethane.

The experiences discussed briefly above have led to the search for more easily synthesized systems. Hoveyda, for example, developed a parallelized approach toward a dipeptide-based library of phosphine ligands for the copper-catalyzed allylic alkylation reaction.[14] In principle, these libraries could also be used in screening for competent catalysts for asymmetric hydrogenations.[15]

Monodentate phosphites,[16] phosphonites,[17] and phosphoramidites[18] have been developed in recent years as versatile classes of ligands for asymmetric hydrogenations.[19] The easy and straightforward assembly of these monodentate ligands allows for the preparation of large catalyst libraries. Monodentate ligands can yield the same or even superior enantioselectivities in comparison to bidentate ligands for certain substrates.[20] A comparison of reactivities for bidentate ligands vs monodentate phosphoramidites also yielded comparable results.[21] Mechanistic work on the Rh-catalyzed asymmetric hydrogenation ultimately confirmed the suggestion that two monodentate phosphite ligands coordinate to the rhodium center.[22]

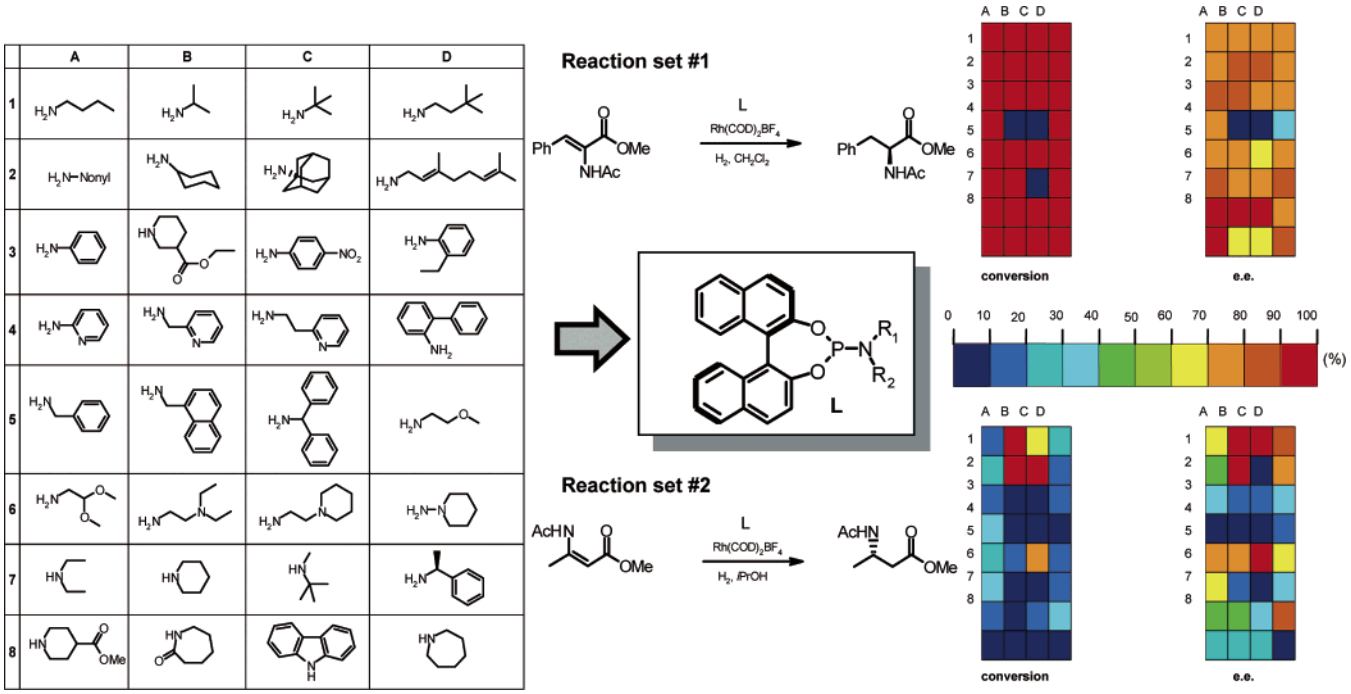
Scheme 3. Setup for Ligand Libraries of Mixtures of Monodentate Phosphoramidites[23]



Recently, researchers at DSM elaborated these findings further, striving for rapid assembly and screening of large numbers of catalysts[23] (Scheme 3).

Their concept utilizes a parallel synthesizer and readily available chlorophosphites as ligand precursors and yields an instant library of crude ligand solutions. Using a parallel reactor in which the ligand solutions are combined with the appropriate metal precursors and the prochiral substrate, DSM can screen a large number of catalysts against a given substrate without the need of having a large number of

Scheme 4. Screening with a Library of Monodentate Phosphoamidites



ligands on stock, thus establishing a very effective virtual ligand library. The protocol described allows for the preparation and screening of 96 different ligands within 2 days (Scheme 4). New phosphoramidites based on the chiral 1,2-diphenyl-diamine motif as introduced by Ding[24] exhibit high modularity and might help extend the combinatorial screening approach even further.

Reetz and co-workers[25] and de Vries at DSM together with Feringa[26] independently described the most intriguing observation in this regard. These groups found an unexpected enhancement in enantioselectivity for *heterocombinations of ligands* in comparison with their homocombinations upon mixing monodentate ligands such as phosphoramidites, phosphonites, or phosphites. Reetz and co-workers achieved enantioselectivities as high as 98% ee for the asymmetric hydrogenation of α-(acylamino)acrylates with such heterocombinations. The best homocombination in the earlier studies achieved only 95.4% ee. The parent homocombinations of the hetero-mixture yield only 93.3% ee and 76.6% ee, respectively (Table 1).

Reetz tested this concept further in the asymmetric hydrogenation of acyl-enamides and dimethylitaconate. In the case of acylenamides, for example, the enantioselectivity of the catalyst is optimal at a 1:1 ratio of both ligands.

The work of de Vries and Feringa focused on mixtures of monodentate phosphoramidites. Here, for example, the enantiomeric excess in the asymmetric hydrogenation of *Z*-*β*-(acylamino)acrylates with ligand **18** was 54% and that for ligand **16** was 80%. A 91% ee was achieved for the same substrate by employing a 1:1 mixture of both ligands (Scheme 5).

In a series of publications, Reetz and co-workers extended the use of heterocombinations of monodentate ligands toward different substrates,[27] introduced the use of achiral ligands as second monodentate ligands,[28] and most recently, described the use of structurally highly diverse monodentate ligands in asymmetric hydrogenations.[29] Experimentally, they used a simple setup consisting of putting eight different vials in one autoclave at a time.[27]

In a joint publication, Reetz, Feringa, and researchers at DSM recently screened a library of 26 selected monodentate phosphoramidites against a diverse set of substrates (Scheme 6). Testing 26 different ligands on 14 different substrates would result in 364 single experiments. However, only a Biotage (formerly Argonaut) Endeavor multireactor, allowing eight single experiments in parallel, was available. The problem of dealing with the large number of experiments was solved by developing a multisubstrate screening procedure for the chosen enamides.[30] Only one GC trace is necessary for separating up to eight different chiral amides using this method, allowing 64 experiments within one single run with the multireactor. In separate control experiments, the same enantiomeric excess was obtained with five different enamides and the catalyst employing ligand **28a** as in the multisubstrate screening.

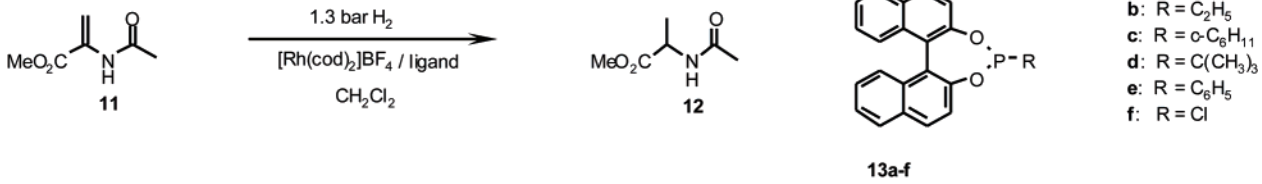
Two ligands in the tested library were identified as privileged.[31] PipPhos **28a** and MorfPhos **30a** showed selectivities between 96% and >99% ee for 8 out of the 11 enamide substrates.[32]

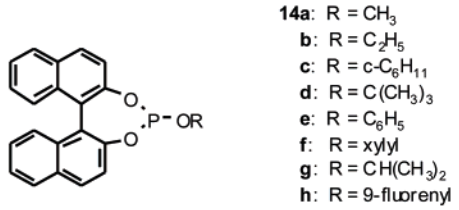
In an alternative approach, Gennari synthesized a library of 16 monodentate chiral tropos[33] phosphorus ligands having a chiral alcohol or amine attached at the phosphorus atom[34] (Scheme 7).

This ligand library yields 16 possible homocombinations and 115 possible heterocombinations. No indications were given on how this large number of experiments was performed. The best result for the rhodium-catalyzed asymmetric hydrogenation of methyl 2-acylamidoacrylate was 55% ee, while the heterocombinations give ee's up to 87%. Interestingly, heterocombinations of two phosphoramidites resulted in lower selectivities as compared to the single ligands. Synergistic effects are only observed upon combining phosphoramidites with phosphites within this ligand library. Optimization of the best combinations resulted in an increase of ee from 87% to 94% ee.

Xiao only found ee's up to 75% and lower selectivities using heterocombinations in the hydrogenation of dimeth-

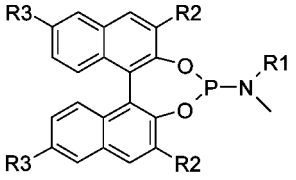
Table 1. Combinatorial Screening of Mixed Monodentate Ligands



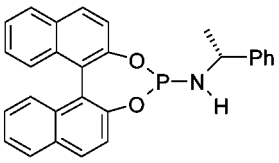


	13a	13b	13c	13d	13e	13f	14a	14b	14c	14d	14e	14f	14g	14h
13a	91.8													
13b	92.6	94.4												
13c	97.9	---	92.0											
13d	97.8	---	94.1	93.3										
13e	---	---	---	75.8	72.8									
13f	---	---	---	*rac*	---	7.4								
14a	81.9	---	96.4	98.0	---	---	76.6							
14b	---	---	---	---	---	---	80.0	83.6						
14c	94.4	---		94.6	---	---	76.6	79.0	94.6					
14d	93.0	---	91.8	---	---	---	89.0	91.2	94.2	95.4				
14e	---	---	---	---	---	---	77.4	80.8	85.6	92.2	78.6			
14f	---	---	---	---	---	---	84.6	---	---	---	---	32.4		
14g	---	---	---	---	---	---	87.2	90.0	94.6	94.8	91.2	---	94.4	
14h	---	---	95.6	97.2	---	---	---	---	---	---	---	---	---	92.4

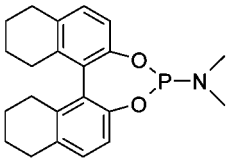
Scheme 5. Mixed Ligands for Asymmetric Hydrogenation of *β*-Aminoacrylates



(S)-**15**, R^1 = Me, R^2 = R^3 = H
(S)-**18**, R^1 = R^2 = Me, R^3 = H
(S)-**19**, R^1 = Me, R^2 = H, R^3 = Br
(S)-**20**, R^1 = Bn, R^2 = R^3 = H

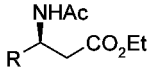


(S,R)-**16**



(S)-**17**

21, R = Me
22, R = Ph

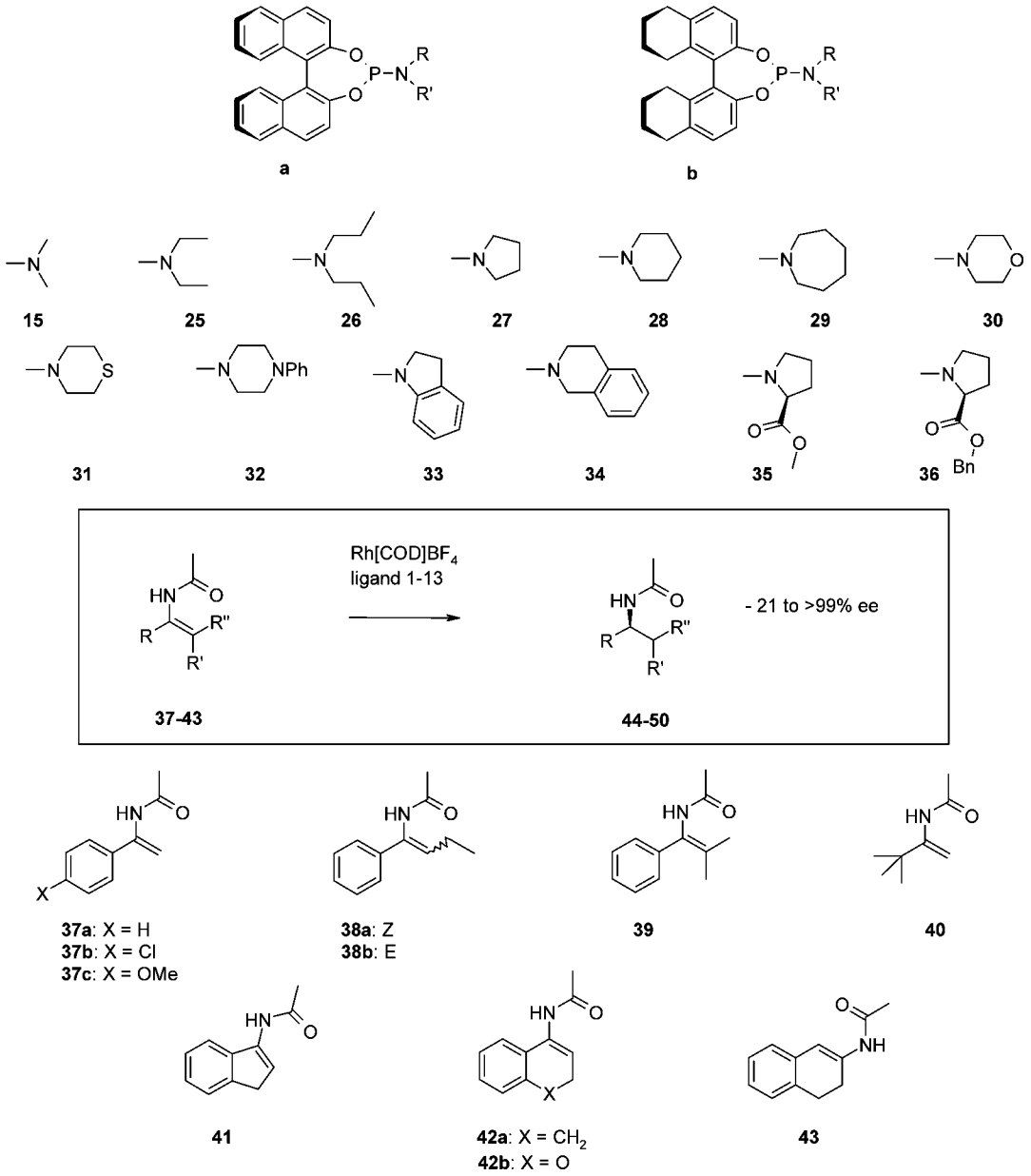


	single ligands	mixed ligands
23, R = Me	up to 80% ee	up to 91% ee
24, R = Ph	up to 78% ee	up to 91%ee

ylitaconate employing a related but somewhat restricted library.[35]

Wills[36] developed a selective ruthenium-based catalyst for the hydrogenation of ketones based on monodentate phosphinites[17] together with researchers from Rhodia.[37] They used a MODDE 6-based statistical experimental design[38] for finding optimal conditions and varied substrate concentration, base concentration, catalyst loading, solvent, and hydrogen pressure. For example, 1′-naphthophenone was reduced to the chiral naphthylethyl alcohol with 99% ee at a catalyst

Scheme 6. Combining Ligand and Substrate Libraries



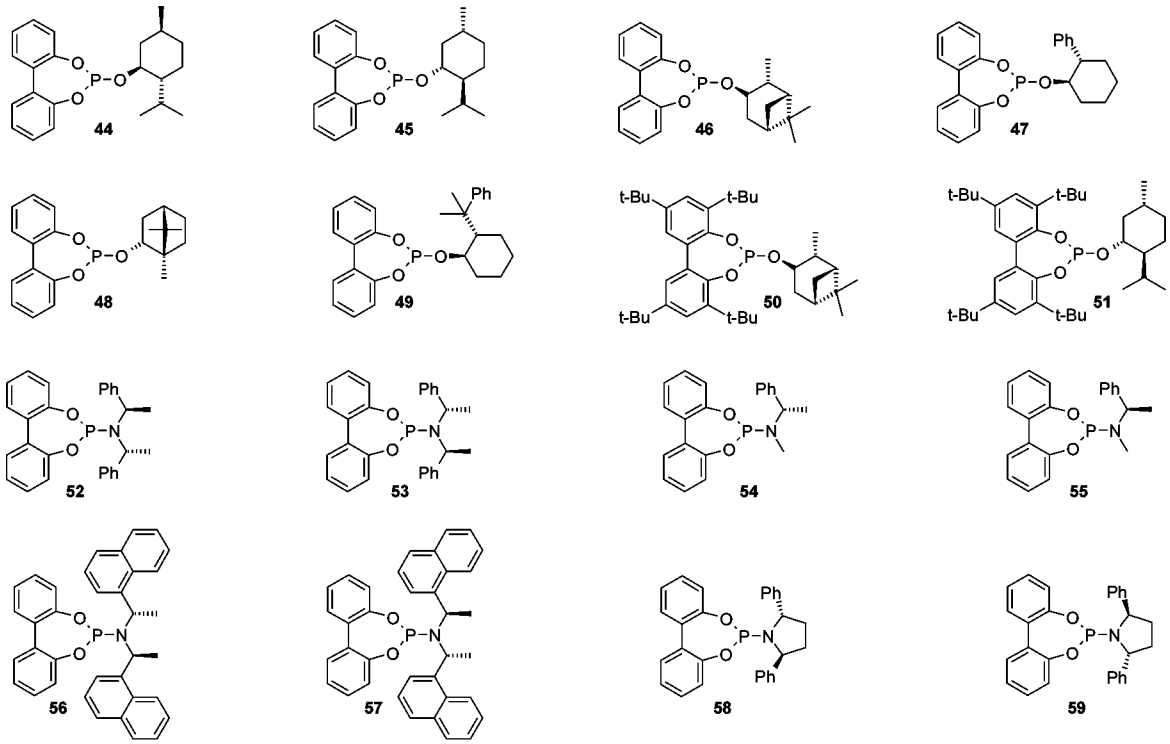
load of substrate-to-catalyst ratio (s/c) = 2000 at 0 °C and 50 bar hydrogen pressure.

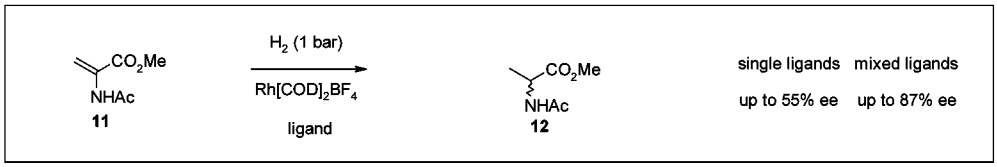
Screening of ligand libraries has not only been used to identify new classes of ligands or ligand combinations. Having large numbers of diverse ligands easily available has made much work related to developing highly selective transformations of novel substrates using asymmetric hydrogenation possible. Besides identifying the best catalysts for known substrates, parallel screening enables one to identify competent catalysts for new and unusual substrate classes. Often enough, this does not occur by inventing new catalyst systems but by finding the right catalyst composition out of already known components.

For example, Goossen and Reetz reported on the asymmetric hydrogenation of enol acetates with monodentate phosphites.[39] The asymmetric hydrogenation of enol acetates results in the formation of chiral esters and constitutes an alternative to the enantioselective reduction of the corresponding ketones. Although some chiral bidentate phosphine catalysts capable of hydrogenating enol acetates with high selectivities have been developed, the substitution pattern at the olefinic function in these cases was restricted to aryl, vinyl, or trifluoromethyl.[40] The hydrogenation of simple alkyl substituted enol acetates remained a challenge. Goossen and Reetz were able to identify a competent catalyst system employing simple monodentate binol-based ligands using sequential single experiments. In theory, 128 single experiments are necessary when testing a ligand library of 16 different binol-derived monodentate ligands on 8 different substrates. The authors, however, chose not to cover all combinations possible but to employ a common iterative strategy. They tested the different ligands first on a single substrate (**3a**), and then tested the two best ligands from this series (**7a** and **7b**) on different substrates (Scheme 8, Table 2).

In related work, Feringa, Minnaard and de Vries tested different monodentate phosphoramidites on different enol acetates and enol carbamates utilizing a Biotage (formerly Argonaut) Endeavor parallel synthesizer. They found excellent selectivities for aryl substituted enol acetates, as well as some enol carbamates.[41]

Scheme 7. Effect of Heterocombinations with Chiral Tropos Phosphorus Ligands





A large amount of experimental data has been accumulated suggesting that a cooperative interaction between the two coordinated ligands is taking place in the systems described above. This interaction might be caused by van der Waals or by dipole−dipole interactions and is therefore intrinsically weak in nature. On one hand, this results in the opportunity to develop large virtual ligand libraries as exemplified above. On the other, it also sometimes makes catalyst definition a time-consuming process, even if massive screening capabilities are at hand, since not *every* heterocombination leads to an enhancement of ee.

A new approach uses stronger ligand−ligand interactions, that is hydrogen-bonding, between the (in principle) monodentate ligands.[42] This allows for more rational design and a more structured catalyst screening. Using this strategy, a bidentate framework is built up at the metal center resulting in a rigid and well-defined structure of the catalyst (Scheme 9).

Both homo- and heterodimers can be formed exclusively depending on the nature of the hydrogen-bonding groups used. The approach shown in Scheme 9 has been demonstrated for rhodium-catalyzed hydroformylations.[43] A first application using chiral versions of this ligand type in asymmetric hydrogenations has also been reported.[44] The concept is not limited to systems using hydrogen bonding. Related ligand systems relying on coordinative interactions have also been reported.[45]

3. Ligand Libraries

In recent years, the explosion in the development of highly selective ligands for asymmetric hydrogenation has resulted in large, still increasing numbers of highly structurally diverse commercially available ligands.

There are now three main independent technology companies—Solvias, JM Catalysts, and Chiral Quest—offering customers broad access to a diverse set of chiral ligands for asymmetric hydrogenation. In addition to these, there are also some smaller companies such as Synkem in France or Stylacats (now part of Phoenix) in Great Britain offering a more selected set of chiral ligands. Using the criterion of commercial availability, five main classes of ligands can be identified: Binap analogues,[46] DuPhos analogues,[47] ferrocenyl-based ligands,[48] P-chiral ligands,[49] and monodentate ligands[16−18,50] (Scheme 10).

Nearly every single company active in the field has developed its own version of Binap.[51] This means a wide variety of Binap analogues is currently available from multiple sources. One drawback in the field of Binap analogues is the necessity of negotiating with many different suppliers of these ligands concerning availability. Another is being certain of freedom to use due to patents still active in the field.

The situation in the area of ferrocenyl-based chiral ligands such as Josiphos is more favorable. Here, one can obtain a wide range of different ligands based on the ferrocene motif from Solvias.

Scheme 8. Screening for Efficient Catalysts for the Asymmetric Hydrogenation of Alkyl-Substituted Vinyl Carboxylates

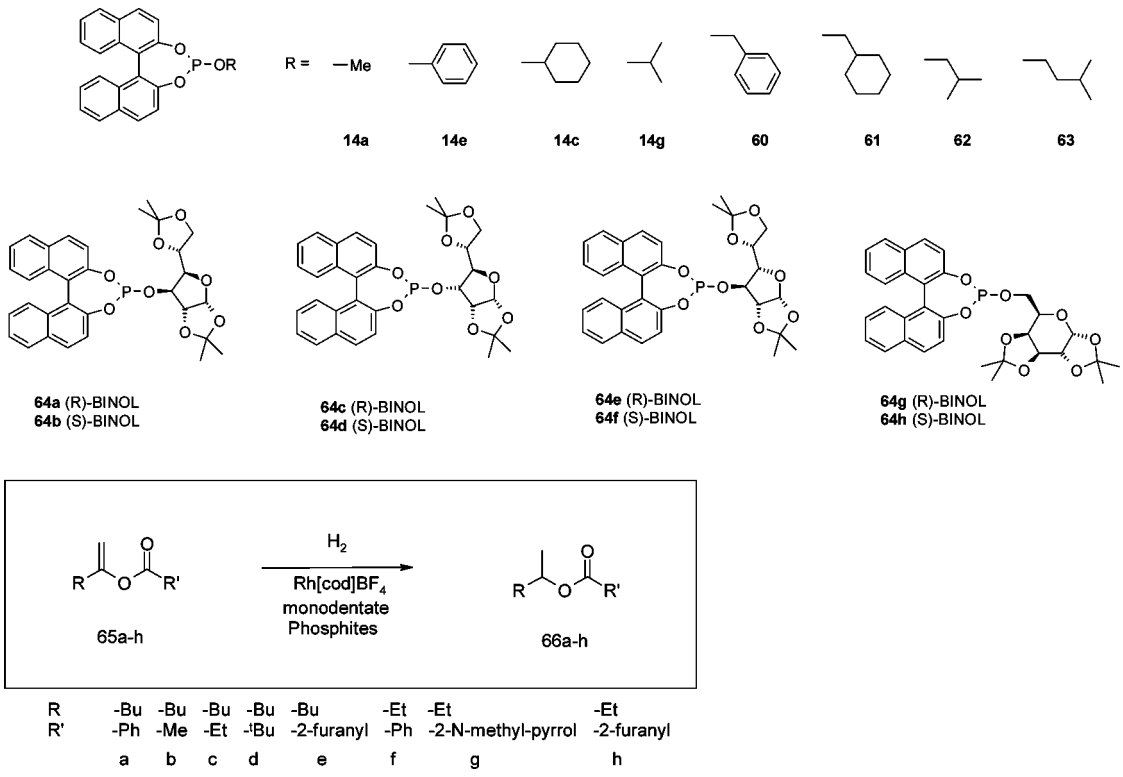
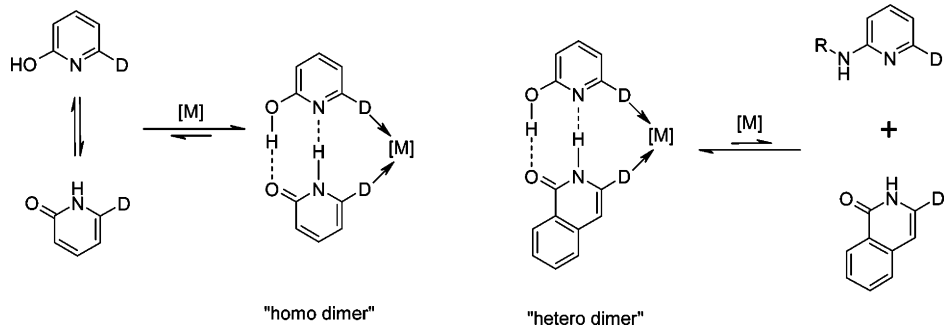


Table 2. Enantiomeric Excesses [% ee] for the Asymmetric Hydrogenation of 3a−h[a]

	14a	14e	14c	14g	60	61	62	63	64a	64b	64c	64d	64e	64f	64g	64h
65a	21.8	25.2	31.6	20.8	39.4	43.8	64.8	37.4	86.4	12.8	39.2	23.0	68.0	17.2	51.2	4.2
65b									73.6	31.6						
65c									74.4	6.2						
65d									41.6	10.4						
65e									94.0[b]	22.0						
65f									80.4	10.8						
65g									71.6	4.8						
65h									88.6[b,c]	34.2						

[a] General conditions: catalyst prepared in situ from $Rh[cod]BF_4$ and 2 equiv of monodentate phosphites **14 and 60−64** in CH_2Cl_2; substrate/catalyst = 200; 60 bar H_2; 30 °C; 20 h. [b] Reaction performed at −20 °C. [c] Substrate/catalyst = 500.

Scheme 9. A Concept for the Assembly of Bidentate Ligands via Hydrogen Bonding



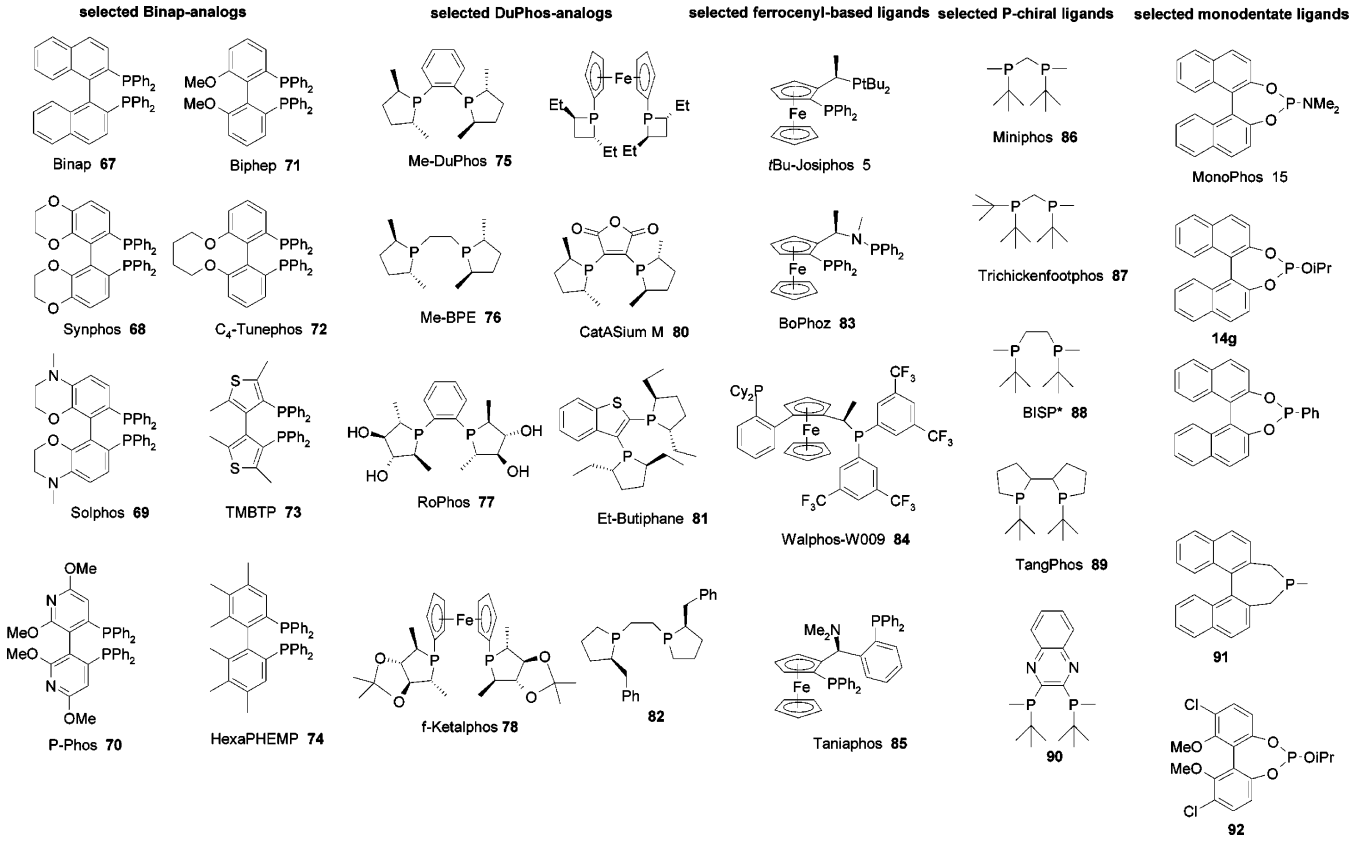
P-Chiral ligands, especially electron-rich systems, have been of great interest in recent years. Imamotos Miniphos and BISP* were the first successful ligands in this class.[52] Elegant mechanistic work by Gridnev and Imamoto[53] has led to much activity on the development of analogues. Access to a diverse library of P-chiral ligands, however, is still limited, with only Chiral Quest supplying some P-chiral ligands for commercial projects.

One main obstacle has been to establish efficient routes to both enantiomers of such chiral P-chiral ligands. One solution to this problem, TrichickenfootPhos—with three hindered quadrants, was developed by Hoge at Pfizer.[54] This ligand was employed in the asymmetric hydrogenation step in the synthesis of the drug pregabalin. A different approach was taken by Zhang during the development of DuanPhos.[55]

Phospholane-based ligands such as DuPhos, introduced by Burk while he was with Dupont, are now available from Dowpharma. However, Solvias,[56] Degussa,[57] and Chiral Quest[58] also supply phospholane-based ligands, which adds diversity to this ligand class.

Monodentate ligands based on Feringa's phosphoramidites[18] are available from DSM.

Scheme 10. Selected Ligands Used in Ligand Libraries



Besides these main classes of chiral ligands, many different specialized ligands are available for commercial purposes. For example, researchers at Degussa in cooperation with Börner have developed some new classes of chiral ligands, for example, bidentate ligands based on a terpene backbone. Unfortunately, not much has been published on the performance and benefits of these ligands.[59]

Ligand libraries for asymmetric hydrogenation employed in screenings for optimal catalysts have, therefore, often included various representatives of the above-mentioned ligand classes. Profiting from the relatively easy accessibility of these ligands on an industrially relevant scale and with industrially relevant prices, researchers started focusing on screenings for new substrate classes or even single molecules.

4. Industrially Relevant Screening Studies

Pagenkopf[60] reported on screening for efficient catalysts for the asymmetric hydrogenation of *o*-alkoxy-substituted arylenamides.[61] The methodology developed gives access to chiral aromatic amino alcohols, which constitutes an important class with applications, for example, as ligands in asymmetric catalysis,[62] resolving agents,[63] and auxiliaries[64] in asymmetric synthesis and as versatile building blocks for many biologically active compounds.[65]

A set of 11 different commercially available ligands together with bis(1,5-cyclooctadiene)rhodium tetrafluoroborate as catalyst precursor were tested in a first screening against two different substrates (Scheme 11, Table 3).

It was observed that Rh complexes of Tangphos **89**, Me-DuPhos **75** and Me-BPE **76** are excellent catalysts for this type of transformation. In further investigations on the substrate scope, different protected or substituted phenolic residues were tested with these catalysts. The enantiomeric excesses achieved employing Me-DuPhos **75** or Me-BPE **76** were relatively independent of the size of the protecting group on the *o*-phenolic moiety (Scheme 12). Pagenkopf used the methodology developed for synthesizing a new class of oxazolines for copper-catalyzed Aldol additions to a dienolsilane.[66]

Researchers at Merck in Rahway were interested in establishing an efficient approach toward α-aryloxy acids and their derivatives.[67] These compounds have important applications in the agrochemical field as herbicides,[68] plant hormones and growth regulators,[69] pesticides,[70] and fungicides.[71] In addition, they exhibit valuable pharmacological properties[72] and serve as useful synthetic intermediates.[73] Choosing **104** as a first simple substrate, they tested 13 structurally different ligands in the presence of [(*p*-cymene)$RuCl_2$] as catalyst precursor[74] (Scheme 13).

Although **73** showed the highest selectivity, Maligres et al. chose Binap **67** because of its excellent cost-effectiveness for further exploration of the substrate scope. Halogen atoms as *ortho*-substituents on the aryl groups tend to decrease the enantioselectivity, while methoxy or methyl substituents at that position do not affect the ee. Strong electron-withdrawing substituents such as -nitro at the *para*-position of the aryl groups lower the selectivity of the transformation. Hydrogenation of a tetra-substituted double bond results in low selectivity.

Merck developed an attractive procedure together with Solvias for the preparation of β-amino acids by a direct hydrogenation of unprotected enamides employing chiral rhodium catalysts.[75−77] An initial screening varying metal source, ligands, and solvent was employed to identify competent ligands for this transformation. It was observed that an acidic solvent is crucial for a successful hydrogenation with 2,2,2-trifluorethanol yielding the best results. Most

Scheme 11. Initial Screening for Effective Catalysts for *o*-Alkoxy-Substituted Arylenamides

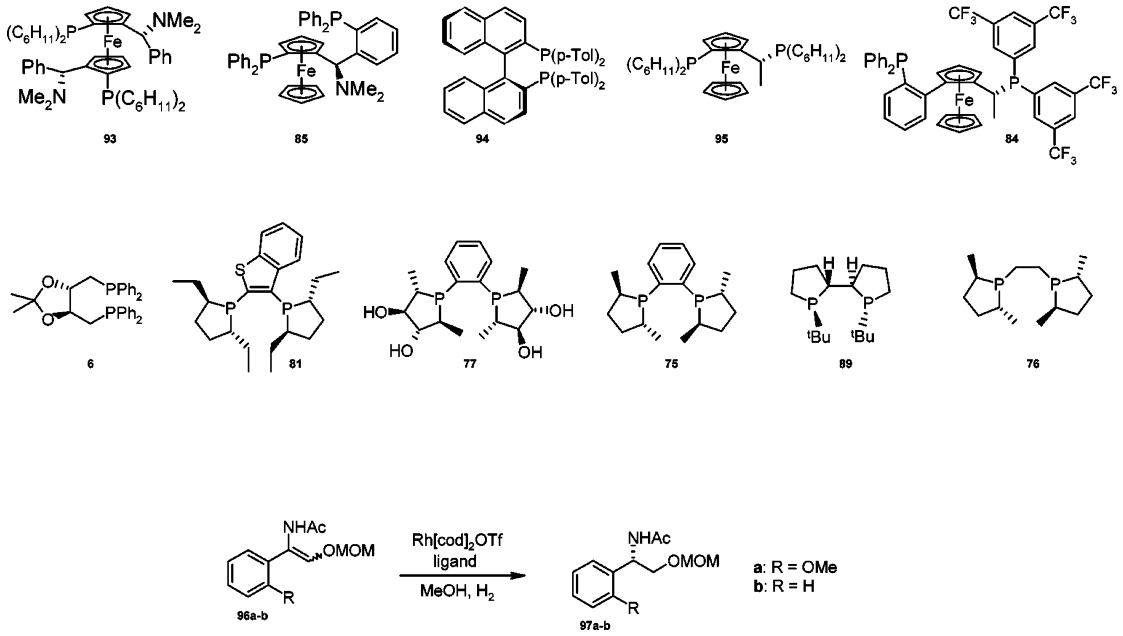


Table 3. Enantiomeric Excesses [% ee] for the Asymmetric Hydrogenation of 77a,b[a]

ligand	**93**[b]	**85**[b]	**94**[b,d]	**95**[b,d]	**84**[b]	**6**[b]	**81**[c,d]	**77**[b,d]	**75**[c]	**89**[b]	**76**[c]
96a	3	7	28	32	39	74	80	89	94.2	94.7	97.8
96b	3	5	32	35	25	84	80	93.5	94.6	95.4	96.2

[a] Conditions: 25−40 °C, 1−14 bar H_2, complete conversions after 24−36 h. [b] Catalyst prepared in situ (1 mol %). [c] Preformed complex used (1 mol %). [d] Opposite enantiomer.

catalyst systems resulted in low yields, low selectivities, or both. Ligands of the Josiphos-type in combination with a Rh source, however, showed exceptional selectivities (Scheme 14). Further investigation into this transformation identified product inhibition, which was elegantly eliminated using in situ Boc-protection of the amine.[78]

Researchers at Merck identified a promising synthetic anthrax lethal factor inhibitor (LFI),[79] as well as a promising synthetic approach based on the successful asymmetric hydrogenation of a *N*-sulfonyl, tetra-substituted α-aminoacrylate (Scheme 15). Having accomplished this, they once again employed the proven strategy of screening a diverse set of commercially available chiral catalysts for this new type of substrate.[80]

The successful asymmetric hydrogenation of *N*-sulfonyl-α-dehydro-amino acids had not reported up to that point.[81] In addition, the hydrogenation of tetrasubstituted α-aminoacrylates is less common due to diminished reactivity.[82] Screening of commercially available ligands together with [(cymene)$RuCl_2$] as metal source identified the Josiphos-type ligand **5** as the most enantioselective with 97% ee. Studies toward determination of the substrate scope established broad applicability for variously substituted substrates. This could be achieved by choosing the right ligand for the specific substrate out of group of ligands **5**, **73**, or **78**. The most crucial observation, however, was a strong dependence of the ee on the solvent choice and the amount of added base. A DOE (design of experiment) study was undertaken to find the optimal reaction conditions in terms of reactivity and selectivity, in which the effects of base concentration, H_2 pressure, and temperature on conversion and ee were investigated. Optimization was accomplished by performing 18 single experiments. The use of this methodology showed that conversion increases with H_2 pressure but goes through a maximum at 50 °C, indicating some catalyst deactivation at higher temperatures. Enantiomeric excess increases with H_2 pressure but decreases with increasing temperature.

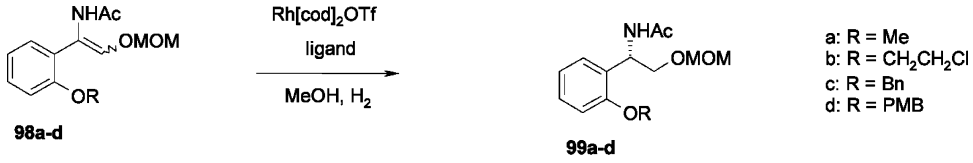
Researchers from Chirotech (now Dowpharma) first reported the use of DOE methods for investigating reaction parameters in asymmetric hydrogenations. They employed MODDE 6 software for data analysis of the results from asymmetric hydrogenation experiments with acetophenone using their Phanephos-modified Noyori catalysts.[37,83] By performing 11 different experiments (Table 4), they were able to deduce the following by computer-based analysis: The variation in selectivity is very slight. In general, lower concentrations and higher pressures enhance reaction rate and selectivity. Higher temperatures increase the rate of the reaction but afford lower selectivities. The rather unusual observation of lower rates resulting from higher concentration was further examined with a different substrate by increasing the ketone concentration gradually from 6% (v/v) to 100% (v/v). It turned out that the observed rate had its maximum at around 30% (v/v).

Yue and Nugent from Bristol-Myers Squibb studied asymmetric hydrogenation as an entry to enantiopure 3-alkyl-piperidines,[2] which are potent pharmacophores with applications in several areas of medicinal chemistry.[84]

They screened 32 different chiral phosphine-based ligands together with 8 different metal precursors resulting in 256 single experiments.[85] As their experimental setup, they used a simple 96-well plate, which was charged with substrate, solvent, and catalysts in a glovebox, sealed, and pressurized with 4.5 bar hydrogen atmosphere. Stirring was carried out using a vortexing unit. Surprisingly, they identified a new iridium-based catalyst system employing the rather flexible BDPP ("skewphos") ligand with sufficient enantioselectivity and activity. Subsequent scale-up to 20 kg scale proved to be unproblematic and proceeded with the same enantioselectivity (Scheme 16).

Vinyl bis(boronates) can be considered as unfunctionalized olefins because of the lack of a second anchor point which

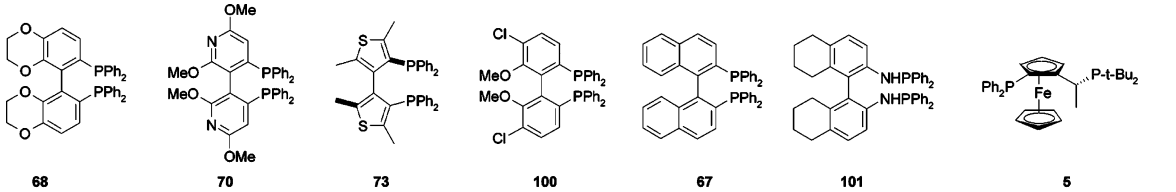
Scheme 12. Dependence of Enantiomeric Excess on Substrate Structure[a]

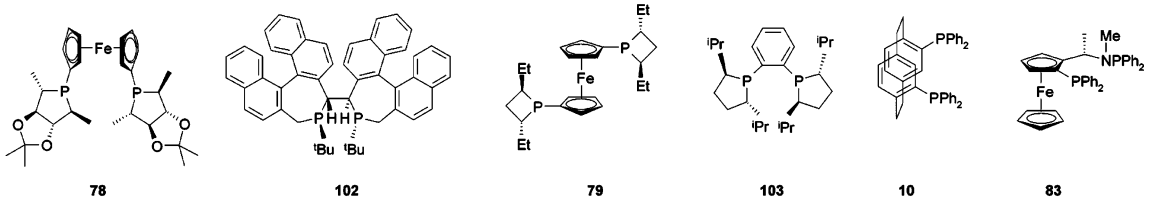


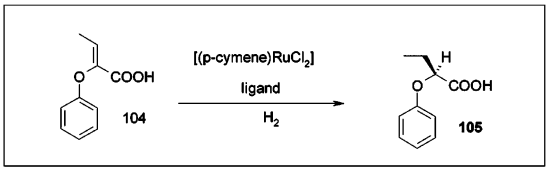
entry	substrate	[%] ee, Ligand **75**	[%] ee, Ligand **76**
1	**98a**	94.2	97.8
2	**98b**	93.8	96.9
3	**98c**	95.4	97.2
4	**98d**	92.8	93.9

[a] Conditions: 1 mol% isolated catalyst used, room temperature, 12 bar H_2

Scheme 13. Results from Screening toward Optically Active α-Aryloxy Acids

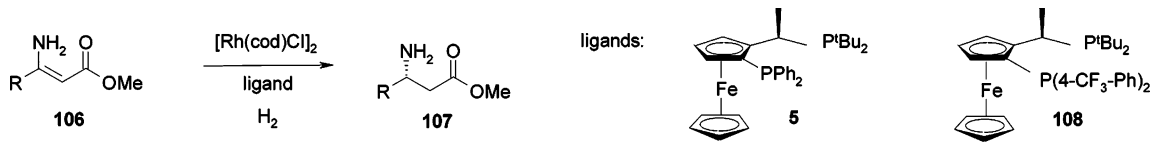






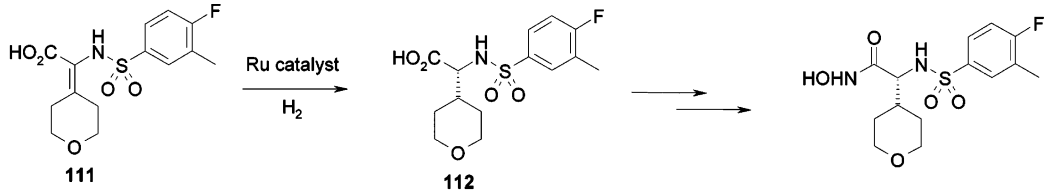
Ligand	**68**	**70**	**73**	**100**	**67**	**101**	**5**	**78**	**102**	**79**	**103**	**10**	**83**
conv. [%]	100	95.4	100	100	100	92.1	98.6	100	100	100	100	100	100
ee [%]	97	91	99	92	93	55	48	1	78	89	21	86	0

Scheme 14. Identifying Catalysts for the Asymmetric Hydrogenation of Unprotected Enamides

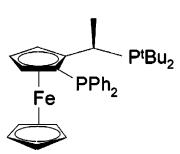


could reduce conformational freedom upon binding to the metal.[86] Morken et al. identified a highly selective asymmetric catalyst with enantiomeric excesses of up to 93% ee in the course of experimentation with the Walphos **84**[87]/$Rh[nbd]_2BF_4$ combination. They provided no details, however, on how they performed the actual screening to identify this catalyst. It appears that they screened with two different metals (Rh and Ir), eight different ligands, and at least three

Scheme 15. Proposed Route for the Synthesis of a Lethal Factor Inhibitor

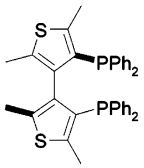


ligands:



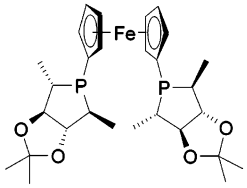
5

Ph_2P-Fc-P(tBu)$_2$



73

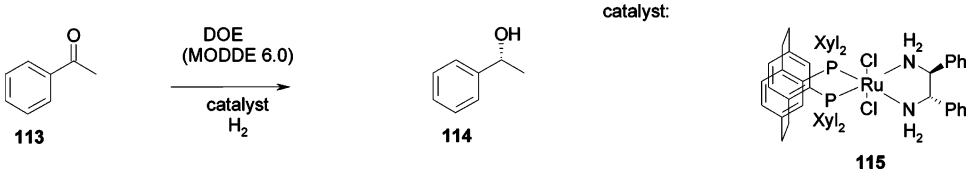
TMBTP



78

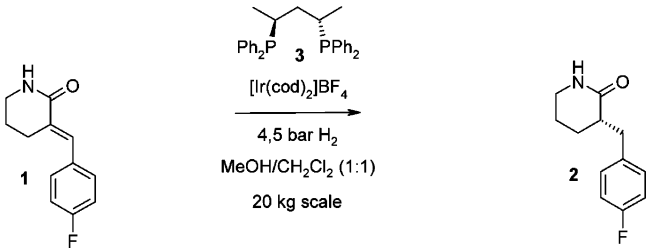
Me-f-Ketalphos

Table 4. Defining Process Parameters Employing DOE



entry	pressure [bar]	temp [°C]	concn ketone [g/mL]	ee [%]	rate (50% conv.) [10^{-6} mol/s]
1	12.7	30	0.4	98.1	6.2
2	2.9	30	0.4	97.5	2.1
3	2.9	30	0.2	97.5	3.0
4	12.7	30	0.2	98.4	11.1
5	2.9	10	0.2	98.8	0.8
6	12.7	10	0.2	98.8	2.9
7	2.9	10	0.4	98.4	0.7
8	12.7	10	0.4	98.7	3.2
9	7.8	20	0.3	98.3	2.9
10	7.8	20	0.3	98.3	4.0
11	7.8	20	0.3	98.7	3.4

Scheme 16. Asymmetric Hydrogenation of 3-(*p*-Fluorobenzylidene)valerolactam

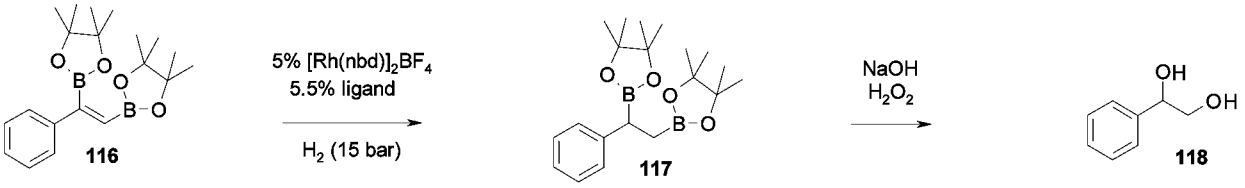


different solvents, toluene being identified as the superior solvent (Scheme 17).

In addition to screening for competent catalysts for new classes of substrates, screening for efficient catalysts for single substrates has been carried out. For example, researchers at Dowpharma developed a new route toward enantiomerically pure sertraline (Zoloft) incorporating asymmetric hydrogenation of a β,γ-unsaturated acid.[3] After intensively screening different ligands and catalyst precursors based on ruthenium and rhodium, they found the Phanephos/Rh combination to be most successful. In comparison, selectivities were disappointing with DuPhos- or BPE-type cationic Rh complexes, with the highest selectivities found to be 20% ee. This finding was rather unexpected, since ligands from the DuPhos-family showed consistently higher selectivities in earlier screenings. They screened 17 different ligands in at least 3 different metal-based environments. In addition, they tested two different ammonium salts as well as the free acid as a substrate. However, they provided no further details on how they performed the actual screening. It seems that they conducted all their experiments in a serial, single manner (Scheme 18).

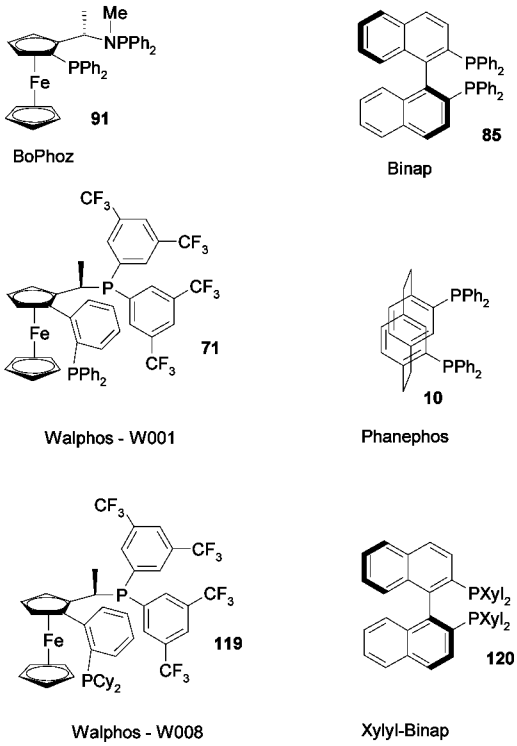
In the course of the evaluation of options toward the synthesis of a peroxime proliferator activated receptor (PPAR) α,γ-agonist,[88] Houpis and co-workers from Eli Lilly developed a highly efficient approach via asymmetric hydrogenation of an α-ethoxy cinnamic acid derivative **120**.[89] They screened more than 250 different catalysts in the hydrogenation, from which the results for 10 catalysts have been disclosed. It was observed that the cationic Rh−Walphos complex **87** showed the highest selectivities with up to 92% ee. The addition of 10% sodium methanolate was essential to achieve complete conversion (Scheme 19). Screens were typically performed in MeOH at 13.8 bar with 2 mol % catalyst precursor and 2 mol % ligand using a Biotage (formerly Argonaut) Endeavor multireactor system.

Scheme 17. Asymmetric Hydrogenation of Vinyl Bis(boronate)[116] *a*



entry	ligand	solvent	% yield	% ee
1	Binap (**67**)	DCE[a]	61	43
2	Phanephos (**10**)	DCE[a]	50	47
3	xylyl-Binap (**120**)	DCE[a]	56	9
4	BoPhoz (**83**)	DCE[a]	58	33
5	Walphos-W001 (**84**)	DCE[a]	82	73
6	Walphos-W001 (**84**)	THF[b]	77	48
7	Walphos-W001 (**84**)	toluene	85	93
8	Walphos-W008 (**119**)	DCE[a]	n.d.	32

Solvents: a) dichloroethane, b) tetrahydrofurane



Legault and Charette[90] discovered a solution for the longstanding problem of asymmetric hydrogenation of substituted pyridine derivatives to chiral piperidines.[91,92] Although asymmetric hydrogenation of quinoline derivatives is feasible,[93] the asymmetric hydrogenation of pyridine derivatives has lagged far behind.[94] To find a solution to this problem, they first tested different pyridine derivatives and limited themselves to an iridium-based catalytic system. They found *N*-acyliminopyridinium ylides[95] to be the only useful substrates under the conditions they tested. Using iodine for activating the iridium complexes proved to be superior to using tetrabutylammonium iodide.[96] Having somewhat defined the conditions for asymmetric hydrogenation, they tested 22 different ligands in the Ir-catalyzed asymmetric hydrogenation of *N*-acyliminopyridinium ylides. They performed the screening by utilizing conventional serial experimentation. Phosphinooxazolines[97] were identified as the most efficient ligands for this transformation (Table 5). Electronic tuning of the ligand class identified resulted in enantiomeric excesses of up to 90%.

5. Screening Examples from Single Substrate Hydrogenations

5.1. Asymmetric Hydrogenation of Candoxatril Precursors

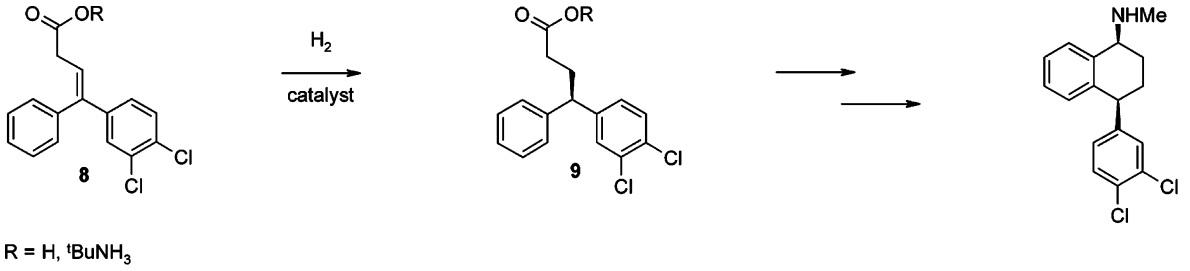
Candoxatril is a potent orally active atrial natriuretic factor (ANF) potentiator developed by Pfizer and is useful for the treatment of hypertension and congestive heart failure.[98] Candoxatril contains a single stereogenic center in α-position to an ester functionality. Only the (*S*)-configured enantiomer shows the desired activity. The essential intermediate of candoxatril, the (*S*)-cyclopentaneglutarate **126**, has been made available using two different enantioselective hydrogenations starting from the unsaturated compound **125**[99] (Scheme 20).

Initial work was devoted to identifying competent catalysts for effecting the asymmetric hydrogenation of **125**.[99a,b] Screening of different ruthenium or rhodium-based chiral catalysts led to the finding that ruthenium catalysts having Binap as a chiral ligand show enantioselectivities of up to 94% ee. Unfortunately, isomerization of the double bond was found to be a serious side reaction, diminishing the yield of the desired product (Table 6).

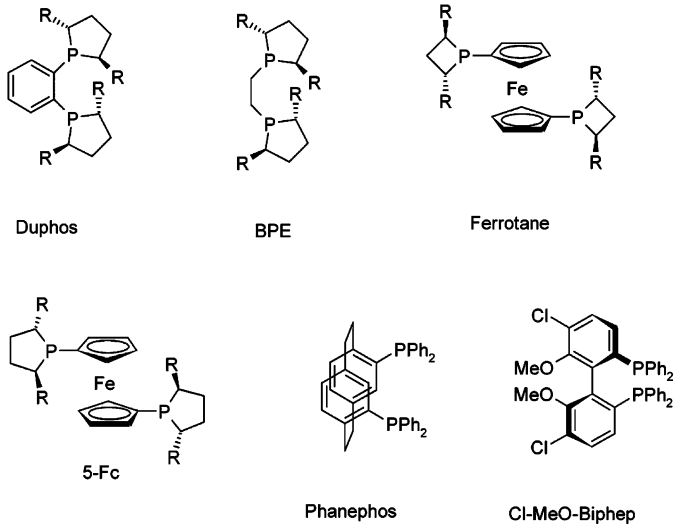
To summarize the initial screening results, ruthenium-based catalysis gave high enantioselectivities but unfortunately also a large amount of useless isomerized material. Rhodium catalysis suffered from lower enantioselectivities and, in addition, from low activities. A decrease in enantioselectivity was observed if the hydrogen pressure was increased to circumvent the lower activity.

One can draw different conclusions from these results to further improve the overall process. If the isomerization can be suppressed by some judicious choice of reaction parameters or catalyst fine-tuning, the ruthenium-based process would be viable. Alternatively, if the selectivity and activity problem within the rhodium system can be solved, this catalyst system would have no problems with isomerization

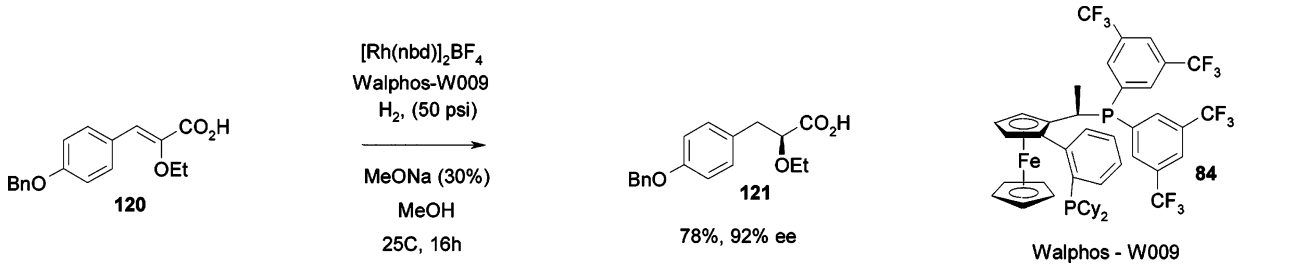
Scheme 18. Screening Results from Ref 3



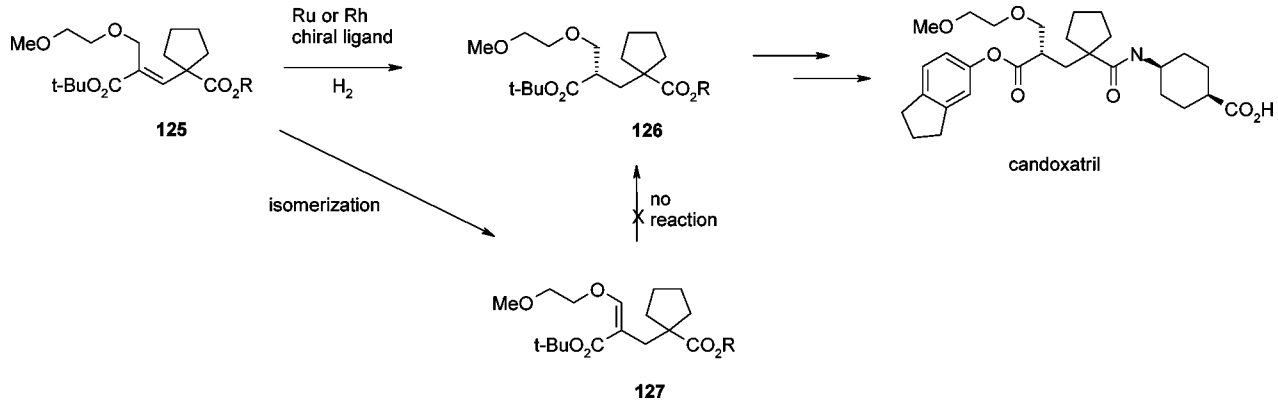
Entry	ligand family	metal	best [%]	ee
1	DuPhos	Ru	44	
2	BPE	Ru	50	
3	FerroTANE	Rh	53	
4	5-Fc	Rh	82	
5	Phanephos	Rh	90	
6	Cl-MeO-Biphep	Rh	36	



Scheme 19. Best System for Asymmetric Hydrogenation of 120, as Identified by Houpis et al.



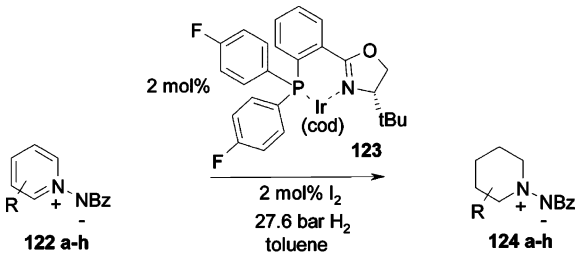
Scheme 20. Synthesis of Candoxatril via Asymmetric Hydrogenation of Intermediate 125



whatsoever. Both approaches have been worked out to yield viable processes.

Burk investigated cationic rhodium complexes with the DuPhos and BPE-ligand family in a cooperation with Pfizer to circumvent selectivity and activity issues related to the rhodium-catalyzed hydrogenation of the candoxatril precursor **125**. They developed a process with both advantages, very high enantioselectivity and no trace of isomerization, thus resulting in an effective procedure for the production of the glutarate **126** (Table 7).

Table 5. Asymmetric Hydrogenations of Substituted Pyridine Derivatives with a Ir−Phosphinooxazoline Catalyst 123



entry	R	yield [%]	ee [%]
1	2-Me (**a**)	98	90
2	2-Et (**b**)	96	83
3	2-*n*Pr (**c**)	98	84
4	2-Bn (**d**)	97	58
5	2-CH_2OBn (**e**)	85	76
6	2-$(CH_2)_3$OBn (**f**)	88	88
7	2,3-Me_2 (**g**)	91[a]	54
8	2,5-Me_2 (**h**)	92[b]	86[c]

[a] Single diastereomer (>95:5). [b] Mixture of diastereomers (57:43). [c] Major diastereomer.

Table 6. Initial Catalyst Screen for the Hydrogenation of 125

entry	catalyst	ee [%]	**2:3** (isom.)
1	$[Rh(cod)Cl]_2$/DIOP (**6**)	24	100:0
2	$[Rh(cod)Cl]_2$/Prophos (**128**)	8	100:0
3	$[Rh(cod)Cl]_2$/BPPM (**3**)	22	100:0
4	$[Rh(cod)Cl]_2$/Binap (**67**)	78	100:0
5	[Rh(cod)-Binap]ClO_4 (**129**)	80	100:0
6	RuHCl[Binap]$_2$ (**130**)	82	92:8
7	RuCl[Binap](*p*-cymene)]Cl (**131**)	94	75:25

Table 7. Optimization of the Rh-Catalyzed Hydrogenation of the Candoxatril Precursor 125[a]

entry	ligand[b]	substrate to catalyst ratio	pressure [bar]	temp [°C]	ee [%]
1	Me-BPE (**76**)	100	20	20	80
2	Et-BPE (**131**)	100	20	20	97
3	Me-DuPhos (**75**)	100	20	20	>99
4	Et-DuPhos (**132**)	100	20	20	98
5	*i*Pr-DuPhos (**103**)	100	20	20	92
6	Me-DuPhos (**75**)	2500	20	20	>99
7	Me-DuPhos (**75**)	2500	5	20	>99
8	Me-DuPhos (**75**)	2500	39	20	>99
9	Me-DuPhos (**75**)	3500	5	45	>99
10	Me-DuPhos (**75**)	10 000	20	20	>99

[a] Conditions: 0.2 M in MeOH. [b] [Rh(ligand)(cod)]BF_4 as precatalyst was used.

In a different approach, researchers at PPG-Sipsy optimized the ruthenium-catalyzed process and solved a different set of challenges.[99d] The original Pfizer process consisted of hydrogenating the sodium salt of **125** with Binap **67** as ligand and yielded only 35% of the desired candoxatril precursor **126** in 99% ee after recrystallization of the cyclohexylammonium salt. Faced with the task of producing at least 2 metric tons of the material, the whole process was reevaluated to find a better economic fit. Due to patent issues, PPG-Sipsy switched from Binap **67** as ligand to the related MeO−Biphep **71** ligand from Roche. The next task was to reduce the isomerization to a reasonable amount so that the yield of the overall process could be improved. Since the rate of the isomerization reaction should not be pressure-dependent, an obvious first approach to improving the **126**/**127** ratio was to simply apply higher pressures. However, at higher pressures, hydrogenation of the isomerization product also occurred, giving the wrong enantiomer and seriously diminishing the optical purity of the product (Table 8).

Table 8. Optimization of the Ru-Catalyzed Hydrogenation of the Candoxatril Precursor 125

entry	ligand	solvent[c]	pressure [bar]	**115**/**116**	yield [%]	ee [%]
1	Binap[a] (**67**)	MeOH	4	78:22	57	97
2	MeOBiphep[b] (**71**)	MeOH	4	78:22	53	97
3	MeOBiphep[b] (**71**)	MeOH	10	92:8	66	85
4	MeOBiphep[b] (**71**)	acetone	4	87:13	nr	98
5	MeOBiphep[b] (**71**)	dioxane	4	88:12	nr	99
6	MeOBiphep[b] (**71**)	THF	4	92:8	nr	98
7[d]	MeOBiphep[b] (**71**)	DMF	4	96:4	nr	99
8	MeOBiphep[b] (**71**)	NMP	4		nr	
9[e]	MeOBiphep[b] (**71**)	THF	4	96:4	69.5	99

[a] As [BinapRuCl(*p*-cymene)]Cl. [b] As MeOBiphepRuBr$_2$. [c] 3:1 solvent/water mixtures. [d] No clean reaction, impurities from decarboxylation of the substrate. [e] Production run (231 kg scale).

A different approach for preventing isomerization would be to try to slow β-hydride elimination of the intermediate ruthenium alkyl complex produced by migratory insertion of the substrate into the ruthenium hydrogen bond by employing a solvent with stronger donor properties. This idea proved to be fruitful. In a 3:1 THF/water mixture, the ratio of **126**/**127** rose from 78:22 (MeOH) to 92:8, yielding the product with high enantiocontrol. With this protocol in hand, PPG-Sipsy conducted a 14-batch campaign with batch sizes of 231 kg. The yield after recrystallization of the cyclohexylammonium salt was improved from the original 35% to a more favorable 69.5%.

5.2. Asymmetric Hydrogenation of a Precursor of the MMP-3 Inhibitor UK-370,106

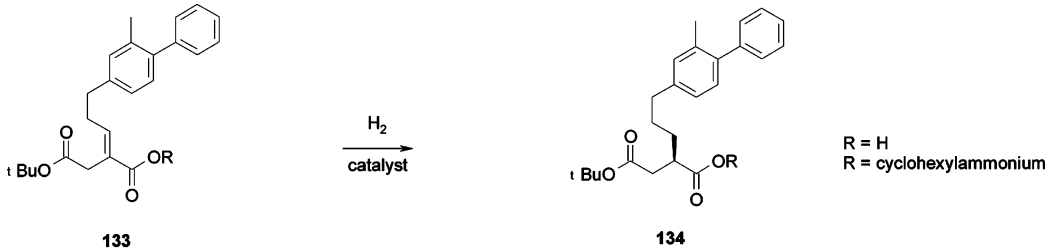
Researchers at Pfizer in collaboration with Chirotech (now part of Dowpharma) investigated the asymmetric hydrogenation of the itaconic acid substrate **133** as an entry to the enantiomerically pure succinic acid based building block of UK-370,106.[100] They screened different substrates such as the free acid and various ammonium or alkali metal salts employing both rhodium- and ruthenium-based catalysts (Scheme 21).

They observed that rhodium catalysts, especially [(*S*,*S*)-Et-ferroTANE)Rh(COD)]BF_4 and [(*S*,*S*)-Et-DuPhos)Rh(COD)]BF_4, showed good performance in the case of the free acid precursor, whereas ruthenium catalysts were most efficient in the case of the ammonium salts. Process parameters such as temperature and pressure were optimized during scale-up. Methanol was found to be the optimal solvent. Catalyst activity improves at higher temperatures and pressures. However, the enantioselectivity deteriorates. Employing the cyclohexylammonium salt together with [(*S*)-Binap-Ru(*p*-cymene)Cl]Cl as catalyst (s/c = 1000) on a larger scale led to a rather moderate ee of 88%. But simple recrystallization from ethyl acetate/methyl ethyl ketone afforded the product in 65% overall yield and >98% enantiomeric excess.

5.3. Asymmetric Synthesis of a Precursor of Pfizer's Pregabalin

(*S*)-(+)-3-Aminomethyl-5-methylhexanoic acid (pregabalin) is a potent anticonvulsant related to the inhibitory neurotransmitter γ-aminobutyric acid and can be used in the

Scheme 21. Selected Screening Results from Ref 100[a]

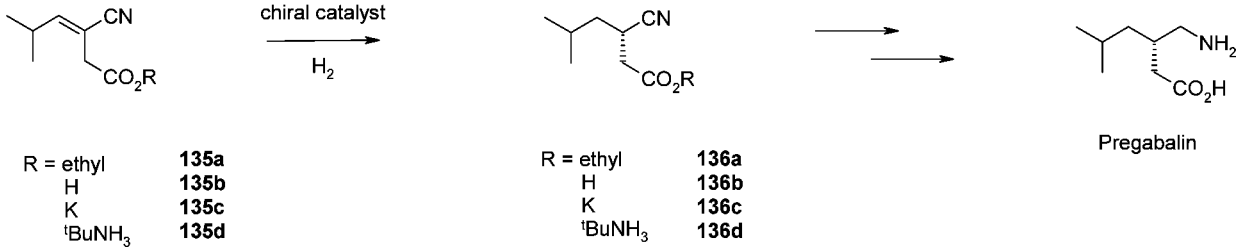


133 134

entry	Substrate, R =	Catalyst	ee[a] [%]
1	H	[(S,S)-Et-DuPhos)Rh(COD)]BF_4	96
2	H	[(S,S)-(Et-FerroTANE)Rh(COD)]BF_4	96
3	Cyclohexylammonium	[(S)-Binap-Ru-(*p*-cymene)Cl]Cl	86
4	Cyclohexylammonium	[(S)-Cl-MeO-Biphep-Ru-(benzene)Cl]Cl	92

[a]conditions: substrate:catalyst ratio 100:1; 4.1 bar H_2; methanol, ambient temperature

Scheme 22. Pfizer/Chirotech Pregabalin Synthesis



treatment of psychotic disorders, seizure disorders, and pain.[101] Since the biological activity resides in the (*S*)-enantiomer, enantioselective routes toward pregabalin were developed early, and the initial preferred route relied on a late stage diastereoselective crystallization of the mandalate salt of pregabalin.[102] This process was still economical. However, problems concerning waste production and throughput caused by the rather low yielding final separation suggested that an even more economically feasible process needed to be found.

Researchers from Pfizer in collaboration with researchers from Chirotech (now part of Dowpharma) identified an efficient process incorporating a catalytic asymmetric transformation as being an attractive option (Scheme 22).[103] Asymmetric hydrogenation of different derivatives of the substituted acrylonitrile **135** was undertaken to identify a viable transformation in terms of selectivity and catalyst activity (Table 9).

Although the selectivities found for the ester were disappointingly low, the free acid and both the potassium and the ammonium salts showed high levels of selectivity with some of the ligands tested. In terms of activity, the salts **135c** and **135d** were superior to the free acid **135b**. Interestingly, the sense of induction changes when changing from the ester **135a** to the other substrates, even though the same ligand was used. Scale-up was conducted by hydrogenating the ammonium salt **135d** with Me-DuPhos as ligand. A catalyst load of up to s/c = 3200 was possible, rendering this new process economically feasible on a technical scale, even though this was a relatively high catalyst loading with a licensed in catalyst.

Pfizer undertook further optimization of the rather significant catalyst costs in this process in house. Research was directed toward the development of new, more effective

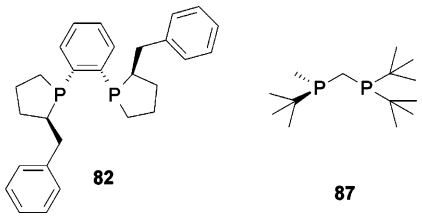
Table 9. Catalyst Screening for Substituted Acrylonitrile 135[a]

entry	substrate	ligand	pressure [bar]	temp [°C]	ee [%]
1	**135a**	(*R*,*R*)-Me-DuPhos (**75**)	6	55	19 (*R*)
2	**135a**	(*R*,*R*)-Et-DuPhos (**132**)	6	55	42 (*R*)
3	**135a**	(*R*,*R*)-^{i}Pr-DuPhos (**103**)	6	55	44 (*S*)
4	**135a**	(*R*,*R*)-Me-BPE (**76**)	6	55	13 (*R*)
5	**135a**	(*R*,*R*)-Et-BPE (**131**)	6	55	13 (*R*)
6	**135a**	(*S*,*S*)-^{i}Pr−BPE (**137**)	6	55	<2
7	**135a**	(*R*,*R*)-Me-FerroTANE (**138**)	6	24	37 (*S*)
8	**135a**	(*R*,*R*)-Et-FerroTANE (**79**)	6	24	7 (*S*)
9	**135b**	(*S*,*S*)-Me-BPE (**76**)	3,3	24	95 (*S*)
10	**135b**	(*S*,*S*)-Et-BPE (**131**)	3,3	24	91 (*S*)
11	**135b**	(*S*,*S*)-Et-DuPhos (**132**)	3,3	24	56 (*S*)
12	**135b**	(*R*,*R*)-DIPAMP (**139**)	3,3	24	72 (*R*)
13	**135c**	(*R*,*R*)-Me-DuPhos (**75**)	4	45	97 (*S*)
14	**135d**	(*R*,*R*)-Me-DuPhos (**75**)	6	24	95 (*S*)
15	**135d**	(*R*,*R*)-Et-DuPhos (**132**)	6	24	97 (*S*)
16	**135d**	(*R*,*R*)-^{i}Pr-DuPhos (**103**)	6	24	24 (*R*)
17	**135d**	(*R*,*R*)-Me-BPE (**76**)	6	24	83 (*S*)
18	**135d**	(*R*,*R*)-Et-BPE (**131**)	6	24	81 (*S*)
19	**135d**	(*S*,*S*)-^{i}Pr−BPE (**140**)	6	24	8 (*S*)
20	**135d**	(*R*,*R*)-Me-FerroTANE (**138**)	6	24	95 (*S*)
21	**135d**	(*R*,*R*)-Et-FerroTANE (**79**)	6	24	85 (*S*)

[a] Conditions: MeOH as solvent, ligands used as either [Rh(ligand)(cod)]BF_4 or [Rh(ligand)(cod)]OTf salts.

ligands for the rhodium-catalyzed asymmetric hydrogenation of **135** to **136**. An additional benefit was the establishment of a proprietary patent basis for chiral ligands, giving more flexibility in commercial catalyst sourcing (Scheme 23). A first generation of DuPhos-type ligands having only monosubstituted phospholane rings **82** was developed by Hoge, resulting in a 96% ee in the asymmetric hydrogenation of the ammonium salt **135d**.[104] In a different approach, Hoge et al. also developed a non-C_2-symmetrical ligand **87** related to Imamoto's BISP* and Miniphos ligands.[52] The asymmetric

Scheme 23. New Ligand Developments for the Asymmetric Hydrogenation of 135d



hydrogenation of **135d** proceeds with this ligand at a catalyst load as low as s/c = 27 000 with 98% ee.[54]

5.4. Asymmetric Production of Synthon A of Novartis' Aliskiren

Aliskiren (SPP100, Rasilez) is a novel nonpeptidic, highly selective, and orally active inhibitor for human renin and is in development as a new antihypertensive agent.[105] The chiral intermediate incorporating the aromatic residue has been termed Synthon A **142** and can be accessed via asymmetric hydrogenation of the unsaturated acid **141**[106] (Scheme 24).

Researchers at Speedel Pharma evaluated different catalysts for the asymmetric hydrogenation of **141**.[87,106] Only the Walphos-system **84**, however, showed satisfactory selectivity together with sufficient activity (Table 10). Scale-up to 12 kg batches with a s/c ratio of 6000 yielded the desired saturated acid in 95% ee and quantitative yield after 21 h.

In a related effort, researchers at DSM developed a process employing their phosphoramidite-based catalyst system for the production of the saturated acid **143**.[107] Initial experiments with MonoPhos as a ligand gave only a disappointingly low 25% ee and low conversion in the rhodium-catalyzed hydrogenation of **141**. Automated screening of different monodentate ligands based on the Monophos motif together with a screening of various additives led to a major improvement in only 3 weeks time. Use of 3,3′-substituted Binol-based phosphoramidites together with simple PPh_3 resulted in 90% ee together with sufficient catalyst activity (Scheme 25). Interestingly, the addition of PPh_3 improves both rate and enantioselectivity in this transformation, increasing the cost-effectiveness of this process considerably.

5.5. Enantioselective Synthesis of the Vitronectin Antagonist SB-273005

SB-273005 is a vitronectin antagonist and has shown activity in an animal model of osteoporosis.[108] Researchers at GlaxoSmithKline developed a concise enantioselective route consisting of a seven-step procedure incorporating an asymmetric hydrogenation for setting the absolute stereochemistry.[109] A limited screening of different catalysts against an itaconic acid derivative provided two different catalysts as possible solutions. Rhodium-based asymmetric hydrogenation with Et-DuPhos **132** as ligand gave 90% ee, whereas a ruthenium−Binap-based catalyst gave 84% ee. The Ru system was chosen because of the lower cost of this catalyst. In addition, results employing the Rh−DuPhos catalyst were not always reproducible. Scale-up was undertaken with a different, but related, substrate. Here, enantiomeric excesses with the Ru system were found to be between 90% and 95%. Simple crystallization of the diacid **149** gave no increase in ee. For that reason, a brief crystallization study was initiated. It was found that recrystallization of the dicyclohexylamine salt improved ee as well as chemical purity to >99%. Direct asymmetric hydrogenation of the dicyclohexylamine salt resulted in material after solvent change and precipitation with >98% ee in 84% chemical yield (Scheme 26). Fifty kilogram batches could be performed with this procedure without difficulty.

5.6. Asymmetric Production of 2-Naphthylalanin Derivatives with the BoPhoz Ligand

Asymmetric hydrogenation of dehydroamino acids was the first commercial application of this technology and resulted ultimately in the Nobel prize for Knowles in 2001.[4e,110] Many different catalysts, both rhodium and ruthenium complexes, have been developed in the meantime, and commercial applications for different unnatural amino acid derivatives have been found.[111] For example, Boaz et al. developed a viable route to Boc-protected 2-naphthylalanin **149** utilizing the ferrocenyl-based ligand BoPhoz **83**, which has found extensive use in the synthesis of pharmaceutically useful agents.[112] Although initial testing showed high enantioselectivities for the *N*-acetyl, as well as for the *N*-Boc, dehydroamino acid, the sensitivity of the downstream products and cost of di-*tert*-butyl carbonate suggested using a late stage transformation to the Boc-protected amino acid. The process, therefore, started with an Erlenmeyer reaction of 2-naphthaldehyde **151** and *N*-acetyl glycine **152**. Subsequent methanolysis of the azlactone **153** furnished the desired starting material **154** for the asymmetric hydrogenation in two steps in 42% overall yield on scale (Scheme 27).

One complication arising from this approach was the presence of impurities in concentrations below the analytical threshold capable of inhibiting the sensitive asymmetric hydrogenation catalyst. For that reason, the initial product was treated with charcoal in dilute acetone solution at ambient temperatures. Process development of the asymmetric hydrogenation step started with screening for the most suitable solvent, since solubility of the starting material was found to be an issue (Table 11).

The best conditions for hydrogenating on scale were found to be at ambient temperature in a 0.37 M (9:1 w/w) toluene solution at 1 bar hydrogen pressure and a catalyst load of s/c = 2000. Boaz experienced mass transfer problems during the production of the first batch in a 22 L vessel due to the low hydrogen pressure employed and the high inherent activity of the catalyst system. This problem was fixed by simply modifying the hydrogen supply to a subsurface addition mode. The acetyl protecting group was removed after setting the stereogenic center by asymmetric hydrogenation. Hydrolysis of the methyl ester **156** and installation of the Boc-protecting group was carried out in a one-pot procedure giving the desired final product. The overall six step process, including a recrystallization step for upgrading the enantiomeric purity, produces Boc-protected naphthylalanin **157** in 33% overall yield and in >99.5% ee.

5.7. Asymmetric Synthesis of (2*S*)-5-Amino-2-(1-*n*-propyl-1*H*-imidazol-4-ylmethyl)-pentanoic Acid

The title compound is a potential target for developing thrombin activable fibrinolysis inhibitors for use in the treatment of conditions such as thrombosis, cancer, and inflammatory diseases.[113] The initial process relied on diastereomeric salt formation use quinidine as chiral amine (Scheme 28).

Scheme 24. Aliskiren via Asymmetric Hydrogenation of the Unsaturated Acid 141

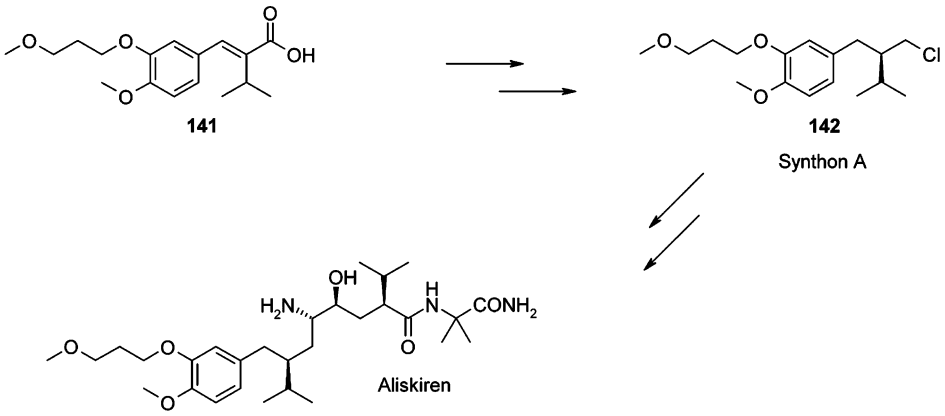
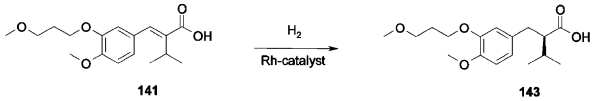
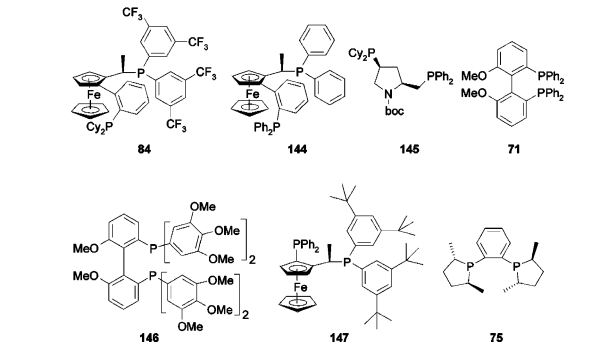


Table 10. Catalyst Screening for Asymmetric Hydrogenation of 141[87,106]



entry	Metal source	ligand	pressure [bar]	temp. [°C]	ee [%]
1	$[Rh(nbd)_2]BF_4$	**84**	50	35	95
2	n.a.[a]	**144**	n.a.[b]	n.a.[c]	79
3	$[Rh(nbd)Cl]_2$	**145**	60	50	80
4	n.a.[a]	**71**	n.a.[b]	n.a.[c]	35
5	$[Rh(nbd)Cl]_2$	**146**	60	50	74
6	$[Rh(nbd)Cl]_2$	**147**	60	30	49
7	n.a.[a]	**75**	n.a.[b]	n.a.[c]	15

acc. to [87]: [a]Rh-based catalyst, [b]between 20-60 bar hydrogen pressure, [c]between 40-50°C.



While this method reliably gave high optical purity of 98% ee, the overall yield of 38% in the resolution step was not suitable for large scale production. In addition, throughput was hampered by the high molecular mass of quinidine in relation to the carboxylic acid **158**. Therefore, an enantioselective transformation was sought to obviate these problems.[114] A straightforward approach would be via asymmetric hydrogenation, since the racemic acid was obtained from the α,β-unsaturated acid **161** by hydrogenation over Pd/C. Several potential substrates for asymmetric hydrogenation were defined and tested in screenings for a competent catalyst (Scheme 29). Interestingly, slight modifications on the substrates resulted in great differences in terms of catalyst activity and selectivity (Table 12).

Process optimization was undertaken with substrate **167**. Unfortunately, the most selective catalyst was not active enough to render the overall process economically feasible. Switching to $[(R,R)^i$Pr-5-FcRh(cod)$]BF_4$ as the precatalyst resulted in an initially lower selectivity of 62% ee but a much higher activity. Most importantly, the enantiomeric excess remained nearly constant on raising the temperature to 70 °C, increasing catalyst activity even further. Thus, the catalyst load was reduced to an economically feasible s/c ratio of 5000. The product was obtained in 76% overall yield with 94% ee after simple recrystallization from EtOAc. The improvement in yield improved the throughput significantly in comparison with the original procedure via diastereomeric salt formation.

5.8. Asymmetric Synthesis of (*R*)-1-(3,5-Bis-(trifluormethyl)-phenyl)ethan-1-ol

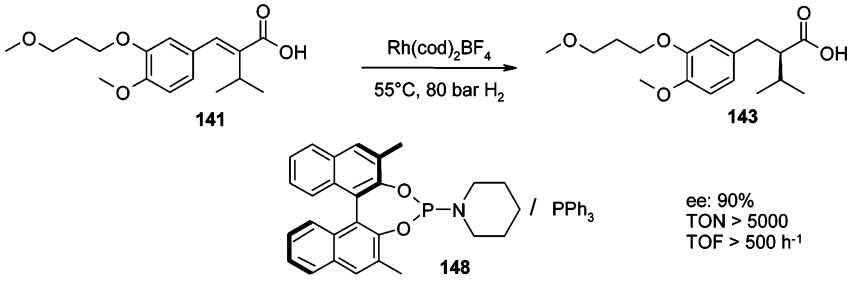
(*R*)-1-(3,5-Bis(trifluormethyl)-phenyl)ethan-1-ol **169** is used as a building block for NK-1 receptor antagonists, for example, in projects at Merck[115] and Schering-Plough.[116] Different groups have reported syntheses of this compound. In addition to reduction with the CBS reagent[116,117] or via enzymatic methodology,[118] transfer hydrogenation[115] and hydrogenation[119] approaches have been developed[120] (Scheme 30).

For example, Solvias has developed a simple method for the hydrogenation of unfunctionalized carbonyl compounds, which complements Noyori's method[37] based on chiral Ru−diamine−bisphosphine complexes.[119c,d] Catalyst screening was performed with 11 different catalysts against 7 different substrates in 65 single experiments with the aid of a multiparallel autoclave. Interestingly, no protic solvent is needed for this transformation. Toluene was used as the solvent of choice. The addition of base was found to be necessary for activation of the catalyst.[119d] Three hundred kilograms of **169** was produced at Rohner after process optimization.[119c]

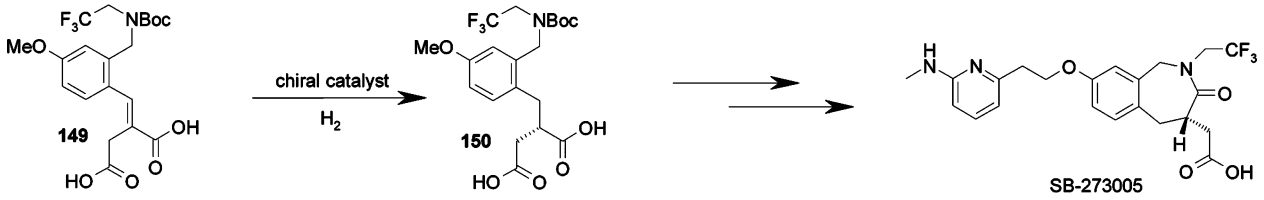
5.9. Asymmetric Hydrogenation of 2-Methylenesuccinamic Acid

Both enantiomers of 2-methylsuccinamic acid **171** are important building blocks for the synthesis of biologically active compounds.[121] The asymmetric hydrogenation of 2-methylenesuccinamic acid **170** would provide direct access to both enantiomers starting from itaconic acid anhydride.[122] Therefore, researchers from Dowpharma decided to develop this route into an economically viable one.[123] In a first step, a ligand screening for the rhodium-catalyzed transformation was performed with high catalyst load of s/c = 100 employing a Baskerville multiwell reactor. Candidates from this screening were then tested at reduced loading. Et-DuPhos **132** not only turned out to have the highest selectivity but

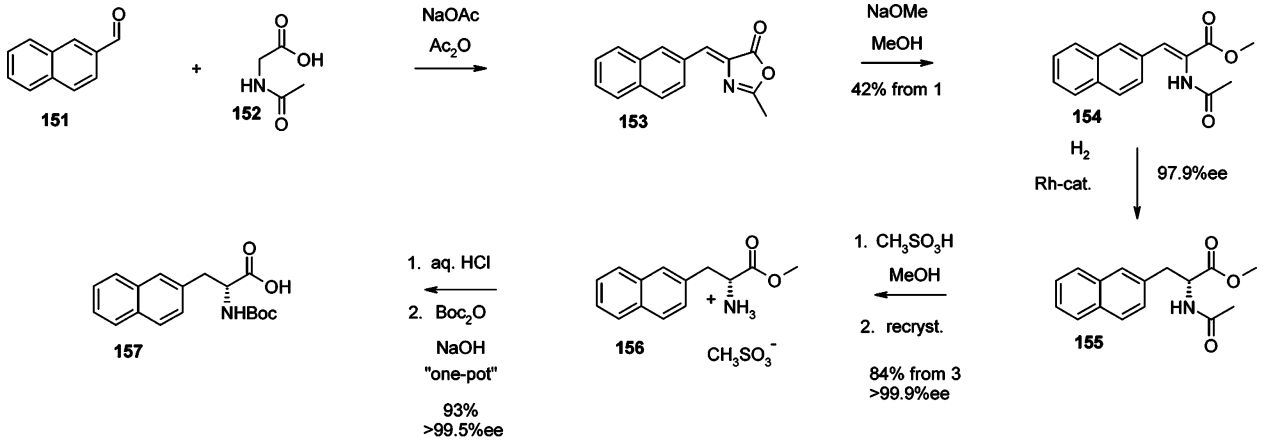
Scheme 25. DSM's Results for the Asymmetric Hydrogenation of Acid 141



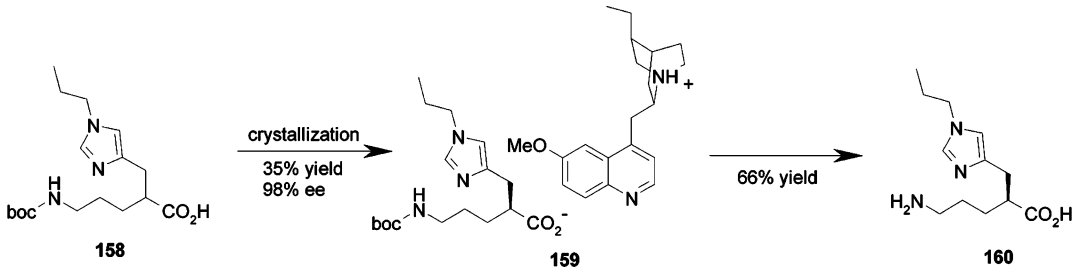
Scheme 26. Asymmetric Synthesis of SB-273005 via Asymmetric Hydrogenation



Scheme 27. Eastman's Route toward (*R*)-*N*-Boc-2-naphthylalanine 157



Scheme 28. Initial Route to 152 via Diastereoselective Crystallization of 150



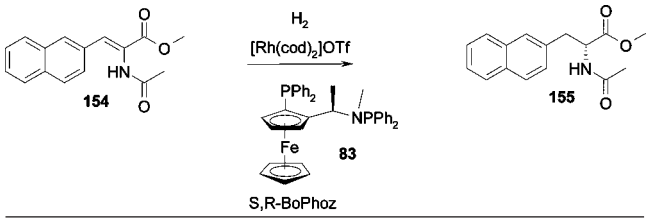
also showed only an insignificant drop in ee at reduced catalyst loading. The selectivity remained stable even at increased pressure and temperature. After removal of the chloride in the substrate by use of a different work up procedure, catalyst activity in the asymmetric hydrogenation was greatly increased, and the catalyst load could be reduced to s/c = 100 000. At that catalyst load, full conversion was achieved in ~8 h with an ee of 96% (Scheme 31).

5.10. Asymmetric Hydrogenation of Other Substrates

The asymmetric synthesis of enantiomerically pure 1-aryl or 1-heteroaryl-3-amino alcohols is a key step in the production of many recent antidepressants, such as fluoxetine or duloxetine.[124] Three different catalyst systems have been shown to give access to highly enriched, optically active intermediate alcohols.[125] Ruthenium-catalyzed hydrogenation of β-ketoesters results in β-hydroxy esters with 90−97% ee depending on the substrate structure,[126] which can be subsequently manipulated to the desired amino alcohols. Researchers at Degussa[127] have demonstrated that asymmetric hydrogenation of an amino-protected ketone can be carried out using Noyori's Ru−bisphosphine−diamine system.[37] Zhang and researchers at Lonza have described an attractive direct route to the alcohol component of duloxetine.[128] Here, rhodium-catalyzed asymmetric hydrogenation of the hydrochloride or the carboxylic acid salt of an aminoketone precursor employing a P-chiral phospholane-type ligand produces the desired component in very high selectivity.

Sannicolo, together with researchers at Chemi S.p.A., developed alternative atropisomeric ligands based on the 3,3′-bisthiophene motif.[129] One application on process scale has

Table 11. Effect of Solvent on Enantioselectivity[a]



entry	solvent	substrate concn [M]	ee [%]	conv. [%]
1	MeOH	0.19[b]	97.2	99.6
2	MeOH	0.37	94.8	87.9
3	acetone	0.19[b]	97.0	99.3
4	acetone	0.37	97.0	100
5	toluene	0.19	97.8	100
6	toluene	0.37	97.4	100
7	EtOAc	0.19	97.2	100
8	EtOAc	0.37	97.2	100
9	TCE[c]	0.19	97.6	99.9
10	TCE[c]	0.37	97.4	99.7

[a] Conditions: s/c = 250, 1 h reaction time at ambient temperatures, and 1 bar hydrogen pressure initially as slurries. [b] Initial reaction mixture was homogeneous. [c] Tetrachlorethylene.

Scheme 29. Substrates for Asymmetric Hydrogenation toward 160

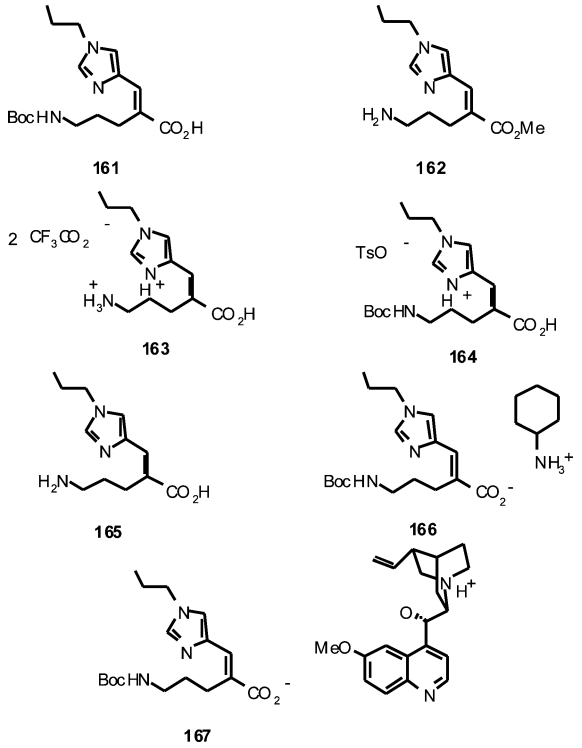
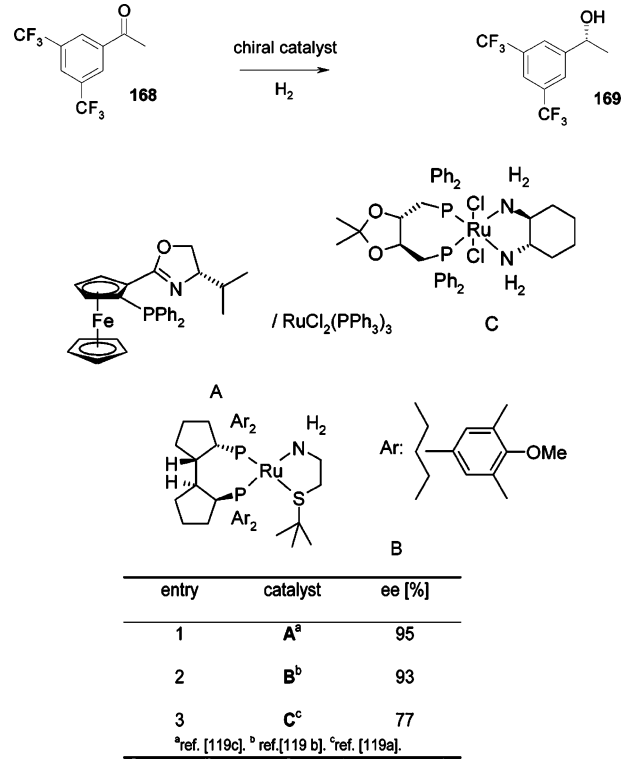


Table 12. Catalyst Screening for Asymmetric Synthesis of 160

entry	substrate	precatalyst	ee [%]
1	**161**	[(*R*,*R*)-^{i}Pr-FerroTANE Ru(methallyl)$_2$]	40
2	**162**	[(*R*)-Binap RuCl]Cl	14
3	**163**	[(*R*,*R*)-^{i}Pr-DuPhos Ru(OCOCF$_3$)$_2$]	83
4	**164**	[(*R*)-Tol-Binap Ru(C$_6$H$_6$)Cl]Cl	77
5	**165**	[(*S*,*S*)-^{i}Pr−FerroTANE Ru(methallyl)$_2$]	56
6	**166**	[(*R*,*R*)-^{i}Pr-DuPhos Ru(OCOCF$_3$)$_2$]	26
7	**167**	[(*R*,*R*)-^{t}Bu-FerroTANE Rh(cod)]BF$_4$	82

been reported for the preparation of enantiomerically pure γ-lactones having important applications in the flavors and fragrances industry.[130,131] Some lactones, for example, whiskey or cognac lactone, can be produced with s/c ratios of up to 2000:1 and enantiomeric excesses of >97% employing the Ru−BITIOP catalyst.

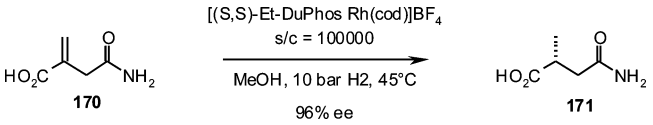
Scheme 30. Various Catalysts for the Asymmetric Hydrogenation of 168[a]



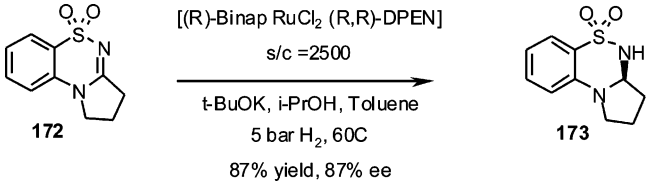
entry	catalyst	ee [%]
1	**A**[a]	95
2	**B**[b]	93
3	**C**[c]	77

[a] ref. [119c]. [b] ref.[119 b]. [c] ref. [119a].

Scheme 31. Asymmetric Hydrogenation of 2-Methylenesuccinamic Acid 170



Scheme 32. Asymmetric Synthesis of S 18986 via Asymmetric Hydrogenation



Researchers from Chirotech, together with Oril Industrie, France, have reported an entry to enantiomerically pure S 18986, a chiral AMPA receptor modulator.[132] They utilized Noyori's catalyst[37] to catalyze the asymmetric hydrogenation of a cyclic sulfonylated imine moiety. Process optimization yielded a system capable of hydrogenating **172** with 87% ee at a catalyst loading of s/c = 2500 (Scheme 32).

Searching for more economically feasible diamine/bisphosphine combinations, researchers from Johnson Matthey Catalysts screened a variety of chiral 1,4-diamines together with Chan's P-Phos ligands.[133,134] Their goal was to achieve efficient asymmetric hydrogenation of isobutyrophenone.[135] This substrate proved to be rather difficult for asymmetric hydrogenation using Noyori's catalysts,[37] with only the relatively expensive xylyl−Binap/DAIPEN combination giving 99% ee. It was observed that the combination of the

unmodified P-Phos ligand with 1,4-diamino-1,4-deoxy-2,3-isopropylidene-threitol, a simple diamine derived from tartrate,[136] gives 95% ee. Surprisingly, the enantiomeric excess was found to be 96% even with racemic amine.

Researchers at Roche were in need of a efficient route to a prophylactic drug for the treatment of diabetes mellitus I and II conditions.[137] The only chiral center necessary was an alkoxy-group α to an ester. Screening for efficient catalysts was performed using various derivatives of Roche's propriety ligand MeO−Biphep **71**,[138] as well as a variety of other ligands. The screening appears to have been performed by placing multiple vials in a single pressure vessel. Sannicolo's tetraMe-Bitiop (TMBTP) **73** was found to be the best ligand for this ruthenium-catalyzed transformation.[129] A process exhibiting both sufficient catalyst activity and enantioselectivity was developed after extensive optimization of pressure, temperature, base additive, concentration, and solvent (Scheme 33).

6. Screening in Industrial Laboratories

6.1. Overview

A number of firms have been active in the area of asymmetric hydrogenation. In general, they tend to describe their work either in Internet presentations or in conference presentations. The number publishing in the open literature is much smaller. Broadly speaking, there are firms such as DSM, Dowpharma, and Lonza, who are active as suppliers of intermediates to the pharmaceutical industry, technology firms such as Solvias and Johnson Matthey, whose business is the sale of catalysts and catalyst know how, technology firms such as Avantium or Phoenix, who are more specialized in process development, and an ever larger number of pharmaceutical companies such as Pfizer, Merck, Hoffmann LaRoche, Bristol Meyer Squibb (BMS), and Lilly, whose interests have often been directed toward early route definition.

An overview of the situation is made somewhat more complicated by a number of acquisitions, such as that of Chirotech, a technology provider with a considerable number of publications, by Dow, a chemical company seeking to expand in the area of fine chemicals. Chirotech then became an integral part of Dowpharma, a supplier of intermediates to the pharmaceutical industry. A further complication is the increasing number of constructions such as the close collaboration of Pfizer with Chirotech/Dowpharma, but here somewhat more in the old Chirotech role of technology provider.

It is interesting to go through and look at the strategies of the different firms, as manifested in their publications, and to correlate these with the screening methods and equipment used.

DSM has published a number of articles based initially on work with Feringa and co-workers and more recently on work with Reetz and co-workers. These publications concern themselves to a large part with discussions of the scope of

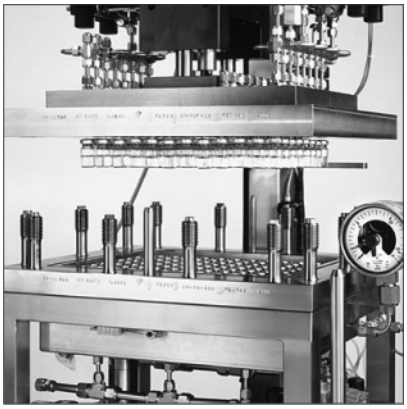


Figure 1. Premex multireactor. Reproduced with permission from premex reactor gmbh.[140]

reactions of monophosphoramidite or monophosphite catalysts[25,26] or with fast methods for generating and screening such systems.[23] In a related piece of work, they looked at ketone hydrogenations using ruthenium catalysts based on cyclometalated amine ligands.[139]

DSM has developed very elegant protocols for the generation of libraries of monophosphoramidite ligands, which very nicely illustrate the advantages and disadvantages of the technology used.[23] It proved possible to automate the synthesis of such ligands in 96-well oleophobic filter plates. This allows removal by filtration of the trialkylammonium chloride produced and precipitated during the reaction. The array of ligands produced, as well as the appropriate metal precursors and substrates, can then be automatically pipetted into a 96-well Premex multireactor (Figure 1).

This type of reactor system allows screening at one temperature and appears to have a common headspace allowing one gas composition and pressure (up to ca. 1500 psi). Reactions are carried out in 5 mL glass ampules. Mixing is achieved using individual stir bars and 96 magnetic stirrers.

A protocol of the type describe above allows the fast generation of a large numbers of ligands. It is, however, limited to systems accessible via a limited number of easily automated, high-yield synthesis steps. For this reason, it generates ligands with a high degree of structural similarity. The necessary simplification of the workup, which leads to somewhat higher values of known catalyst poisons such as chloride, has been observed to lead to a reduction in activity and selectivity. The trends observed, however, appear to be the same as those seen with highly purified ligands. A fast scale-up of the results obtained is only possible due to the extremely high similarity of the systems and the relatively low price of the ligands, which allows reasonable catalyst costs to be achieved with less optimization than that necessary for expensive bisphosphine catalysts.In another DSM publication,32 a library of 20 monophosphoramidite ligands was generated, and their utility as asymmetric hydrogenation catalysts was investigated. A Biotage (formerly Argonaut) Endeavor multireactor (Figure 2) with eight reactors was used to do the screening (75 psi, room

Scheme 33. Asymmetric Hydrogenation of an α-Alkoxy Acid

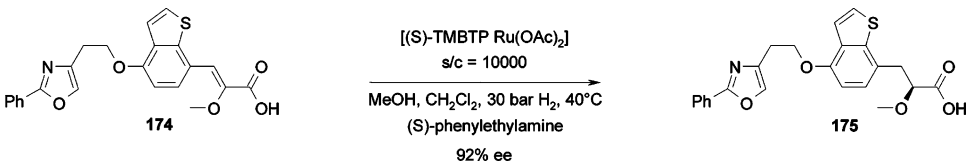


Figure 2. Biotage (formerly Argonaut) multireactor. Reproduced with permission from Biotage[141]

temperature). α-Dehydroamino acid esters were found to be effectively hydrogenated. An interesting one-pot, multisubstrate procedure for the rapid screening of such esters was developed to do this. This could be accomplished because it was shown that up to eight racemic *N*-acylamines could be analyzed in a single chiral GC run. As a cross check, five enamides were separately hydrogenated to the appropriate chiral amines, and it was shown that the individual data corresponded to those from the parallel experiments.

This type of reactor system allows the reaction parameters and data to be handled using a personal computer. Pressures of up to 500 psi, temperature, and the rate of stirring can be varied separately for each reactor (working volume 1−5 mL liquid or solid, ca. 20 mL gas phase). It is possible to do individual kinetic treatments for each autoclave based on hydrogen uptake.

The growth and changes of Dowpharma provide an interesting insight into the dynamic of this research area. Here one needs to start with the results reported by Chirotech, which was a very active technology provider before being taken over by Dow. For example, the development of a process for the hydrogenation of an unsaturated acid (target molecule candoxatril) was described in a very typical publication from the end of the 1990s.[99c] Screening of ligands and metal precursors was done in at 1 mM scale in 50 mL Parr autoclaves. This was followed by an optimization of reactions parameters such as pressure, temperature, substrate-to-catalyst ratio (s/c), and additives. The first stages of scale-up were also described: to 1 kg in a 7 L autoclave followed by 12 kg in a 200 L reactor.

A more detailed workflow was described in 2003 for the hydrogenation of acetophenone derivatives.[83] Screening was done in 50 mL pressure vessels (presumably from Parr, as in other publications). An experimental design was carried out to optimize reaction parameters such as *T*, *P*, and concentration of substrate. The reaction was scaled up to 60−80 g in a 600 mL glass-lined reactor with an overhead stirrer. Scale-up to 1 kg was done in a 10 L reactor at 100 psi. In a procedure typical for industrial laboratories, calorimetric studies were carried out to understand the kinetics of the heat flow and the exothermicity of the reaction.

At this point, publications begin to appear under the Dowpharma name. The workflow, for example, for the hydrogenation of dihydropyrrolobenzothiadiazine,[132] remained unchanged. Screening was done in a "multiwell vessel", presumably a Baskerville multireactor as described below, and the results were confirmed in "single-well vessel",

Figure 3. Baskerville multireactor. Reproduced with permission from Baskerville Reactors and Autoclaves limited.[142]

Figure 4. Symyx parallel polymerization reactor. Reproduced with permission from Symyx Technologies, Inc.[144]

presumably a glass-lined reactor as describe above, with improved stirring capability. Factorially designed experiments were used to optimize conditions. In another procedure typical for industrial labs, the parameters were "manually adjusted" to optimize the economics of the process.

The hydrogenation of 2-methylenesuccinamic acid was described in another publication from this period.[123] Here screening was carried out under standard conditions (time, *T*, *P*) in a Parr 50 mL reactor or a Baskerville multiwell reactor (Figure 3). A precise description of the multiwell reactor used in this study was not given. The systems consist of 10 30-mL reactors, which can be pressured up to 1450 psi. It appears possible to individually charge and sample the reactors in some of the equipment modifications. Use of higher automation, for example, liquid handling systems, appears difficult. They are designed for use with a magnetic stirrer or stirrer/hotplate.

Joint publications from Dowpharma and Pfizer have focused on route discovery. The hydrogenation of β-substituted itaconic acid derivatives was carried out at 100 psi in 50 mL glass-lined Parr microreactors.[103b] The hydrogenation of an imidazole-substituted acrylate was investigated in another study.[114] Possible substrate modifications (salt formation, esterification) were investigated in addition to a screening of possible metal/ligand combinations in a process typical for process definition.

Dow has published separate work where they have looked at asymmetric hydroformylations using chiral chelating phosphites.[143] One point of particular interest in this study was the use of multisubstrate screening. Selectivities for a given catalyst were tested on three substrates (styrene, allyl cyanide, and vinyl acetate) simultaneously. The appropriate controls were carried out to make sure that the substrates do not influence one another. This work was carried out in a Symyx parallel polymerization reactor PPR-48 (Figure 4) with 48 catalysts and 3 substrates (144 separate reactions). The system is built into a drybox, allowing all operations to

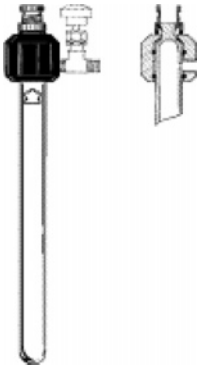


Figure 5. Griffin-Worden pressure vessel. Reproduced with permission from Kimble/Kontes.[146]

be carried out under inert atmosphere, and allows reactions up to 500 psi. The reactors (3−5 mL working volume) can be individually heated, mechanically stirred, and pressurized,[145] Reaction parameters and data are handled using a personal computer. Reagent handling is done robotically. According to patent descriptions, calorimetric data, as well as gas uptake data, can be obtained.

Pfizer itself published a series of studies centered around a new pregabalin synthesis.[104b] In addition, new P-chiral catalysts were described, and their substrate scope was investigated.[54] In these screening studies, the hydrogenations were carried out in Griffin−Worden pressure vessels (Figure 5), which depending on material (borosilicate or quartz) can be used up to 250 psi. This is a typical example of glass reactors often used in early phases of screening. They are relatively inexpensive and easy to use. They tend to be stirred using magnetic stirrers and stir bars and can have problems with mass transfer, due to the relatively limited gas−liquid exchange surface.

The Pfizer efforts seem typical of the trend among pharmaceutical companies to establish their own groups in this area. Eli Lilly, for example, has published exploratory screening work (metals, ligands, and solvents) for α-alkoxycinnamoyl derivatives using a Biotage (formerly Argonaut) Endeavor multireactor system.[89]

Bristol-Myers Squibb (BMS) describes a screening protocol for the hydrogenation of a 3-alkyledenelactam[2] using various metals and 32 P-ligands. The catalysts were synthesized in 1 mL vials in 96-well plates in a drybox using a Gilson liquid handler. The hydrogenations were carried out in a less complicated Symyx reactor system (as compared to the PPR-48). This system consists of a 96-well plate with an airtight cover. It has a common headspace (e.g., only one gas composition and pressure are possible at a time) and one common temperature. Screening over these variables has to be carried out sequentially or by having more than one apparatus, with the attendant infrastructure, available. Stirring was carried out in this study using a locally modified commercial vortexing unit. The reactions were carried out at 65 psig at temperatures between RT and 40 °C. A subsequent scale-up in 20 kg scale in a 400 L reactor was carried out.

Merck published work describing the hydrogenation of unprotected enamines.[75] Screening of metals and ligands was carried out serially at 100 psi and 50 °C using catalysts provided by Solvias, a technology provider.[147] The equipment used, however, was not clearly described in the supplementary material.

In another study, however, the Merck group described a broad screening for catalysts effective in the hydrogenation of α-aryloxy acids.[67] Here, glass vials with pierced septum caps were charged with the aryl enol ether substrates and placed in a glass pressure vessel and hydrogenated at 25 °C and 90 psi. Parallel experiments are, in principle, possible, because multiple vials can be put into one glass reactor. However, the mass transfer problems in such systems are considerable. Selectivity screening is possible, but only in systems that do not depend strongly on the partial pressure of hydrogen in the reaction mixture.[148] In a very recent publication,[149] the Merck group published a study describing the route definition for a β-amino acid pharmacophore. Here, the scale-up to 24 L scale (2 × 12 L, 150 psi, 60 °C) was briefly described as part of the synthetic efforts. This group has been very productive, and it is to be expected that a description of a scale-up to commercial quantities will appear soon.

To round out the picture, it is useful to look at the efforts of some less active groups (in the sense of publication) in the area. For example, Johnson Matthey, a technology provider,[150] published a study describing catalyst development for ketone hydrogenation. The reactions were carried out in a 50 mL Parr autoclave at 150 psi and 25−30 °C.[135]

PPG-Sipsy described studies done for a chiral succinate intermediate for candoxatril.[99d] Limited studies were carried out to find an appropriate ruthenium precursor to generate a catalyst using an available ligand. Solvent and pressure were optimized as part of scale-up. To commercialize, a commercial supplier of the appropriate metal precursor had to be found. Scale-up to a 4 m^2 reactor was described. Two tons of product were made in 14 231-kg batches. The s/c ratio was held low to minimize the risk of a failed batch. The final purity was achieved via recrystallization.

Lonza published an interesting overview containing a number of studies where commercial scale-up was carried out.[151] Typical for industrial publications, the studies are focused on technically successful projects, which were canceled due to cost or marketing reasons. Nonetheless, the workflows described and problems considered are quite instructive. The article discusses the main commercial constraints, process cost and implementation time, in a very compact way. Factors such as catalyst selectivity and availability (both in the sense of quantities needed and in the sense of right to use) are crucial here. As is rightly pointed out, it is sometimes better to achieve a lower ee with a commercially available catalyst and bring up the ee in a later step, than to try to develop the "perfect" catalyst in the limited amount of time available for development. Other constraints, such as the use of existing equipment to minimize investment and accelerate implementation, are also logical consequences of the commercial constraints but are also sometimes paid for in reduced ee or yield.

Lonza described a straightforward ligand screening for their biotin process, as well as the parameter screening and optimization (where they drop pressure to use existing equipment). They did a large number of pilot plant runs in a 630 L reactor and then scaled up once again in a 10 m^3 vessel (1500 kg batches). Here they reduced the s/c ratio to minimize the risk of a failed batch. The problems in obtaining the necessary quantities of ligand for commercial production are also addressed. In this case, the problem was solved by in house development. This option is unfortunately usually not available in projects with very tight time constraints.

In the same account, Lonza described a similar workflow for their dextrometorphan process. Here they emphasized the

process optimization and its effects on the catalyst activity and selectivity. A number of compromises, such as a change in the substrate salt used, were made to achieve good results. Stable process conditions could be found for runs in a 100 L BUSS reactor. This is a type of loop reactor, which uses a gas−liquid ejector to achieve good mixing and mass transfer. Technically, it is an alternative for the stirred tank reactors used in most of the other studies mentioned here. A product with ee's in the lower 80s was obtained, which could recrystallized up to ca. 98% ee.

6.2. Screening at BASF

As one can see above, it is difficult to give a good description of the work being done in industrial labs concerning screening and scale-up. Information is often only to be found in websites or to be heard in nonpublic lectures by the firms involved. As one would expect, these types of presentations also tend to focus on commercial aspects of the work being done. We would like to help broaden the knowledge base in this area by describing our own efforts and their motivation.

In the BASF Chemical Research and Technology Laboratory, there are a number of specialized groups, including ones dedicated to homogeneous catalysis. The authors are members of a group specialized in the development and use of homogeneous catalysts in technical processes.

One example of such homogeneously catalyzed processes is the hydroformylation of olefins, where the BASF has more than a million tons of production. The resultant aldehydes and alcohols are the basis for value-added chains leading to a variety of products. Due to its importance, hydroformylation has been intensively researched for decades. The cost pressure for such commodity chemicals has led to the development of extremely efficient catalysts and processes. It has also allowed us to build up a considerable amount of know-how and infrastructure.

How does a company with this type of background deal with a complex technology such as enantioselective hydrogenation, where there are literally thousands of options in the literature? We started by trying to structure the available ligands according to criteria of interest to us, that is, according to the patent situation and their availability in technical quantities. It quickly became clear to us that a large number of relatively good solutions were already available and could be accessed via technology suppliers. In the short term, it made more sense to license in the ligands needed rather than develop them in house.[152] Another factor critical for success in such reactions is the availability of technical quantities of metal precursor complexes in the appropriate purity and with the appropriate batch-to-batch reproducibility. Finding appropriately specialized suppliers also solved this problem.

We decided to concentrate on methods for fast screening and scale-up. This, of course, meant optimizing our equipment and workflows for this type of problem. In approaching such problems, one has to have a relatively good idea of what to test first, as one rapidly comes into a regime where too many options must be tested. One needs to be able to test under conditions suitable for available reactors to help optimize the economics. And, occasionally, one has to understand exactly what went wrong the first time to find a good solution quickly. An important component for success is a highly trained staff, because the equipment and workflows are relatively complex and need a fair amount of attention. All of these factors played to our traditional strengths in organometallic chemistry, catalysis, and process technology.

Figure 6. Chemspeed Accelerator.

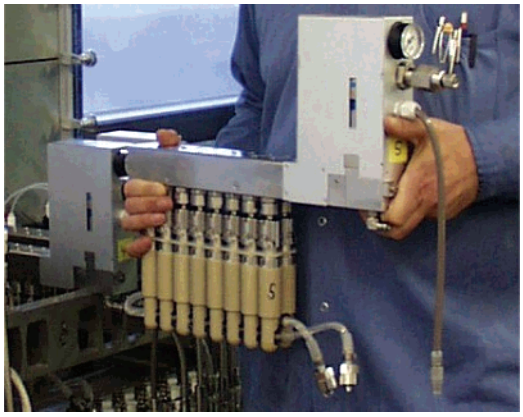


Figure 7. Reactor block with 16 reactors.

On the equipment side, we decided to work with Chemspeed. After intensive discussion and testing, they were able to supply us with an instrument capable of running 96 parallel reactions at pressures up to 100 bar (1450 psi).

Among the commercially available parallel synthesis machines, the Chemspeed Accelerator (Figures 6 and 7) is, in our opinion, one of the ones with the highest flexibility with respect to variation of variables in a large number of individual reactors. Complex experimental designs are made possible by a robotic dosing system. This allows the screening of a relatively large reaction space in a relatively short amount of time and using a relatively small amount of material. Up to 96 experiments can be carried out with as little as 1.5 mL reaction volume per reactor. Two temperatures, six pressures or gas mixtures, and variables such as metal, ligand, and solvent can be varied. We have done comparisons of reactions done with the vortex mixing in the Accelerator and reactions done in mechanically stirred 100 mL autoclaves and not found any mixing or mass transfer problems.[153]

To achieve fast turnaround times, we had to debottleneck our analytical methods. One example of what can be done involves the use of GC-methods such as column switching in isothermal mode, allowing the determination of 96 ee's

Figure 8. Premex miniautoclave. Reproduced with permission from premex reactor gmbh.[154]

overnight. In general, we have found that dedicated GCs and HPLCs are necessary to handle the output of such screening machines. Other factors are also of importance. It is usually necessary, for example, to develop an analytical solution that is amenable to parallel screening. This must usually be done in a very short period of time for the types of problems that we are interested in. Here, it is extremely useful to have a specialized analytical department, who do the method development and then transfer the method to our screening group.

Once one has a hit in the screening runs, a scale-up into small, well-understood stirred reactors (Figure 8) is carried out to quickly do kinetic experiments and generate the data for scale-up into technical reactors. Somewhat more material is of course necessary for these types of experiments. However, such reactors are theoretically well understood, and the data can be modeled easily, as long as all of the appropriate precautions concerning mass transport limitations, mixing energy, etc. have been taken care of.

A few more practical factors also have to be considered at this stage. We have found, for example, that the technical runs are sometimes very dependent on the exact equipment available. This leads to questions of material compatibility, catalyst initiation times, restrictions in dosage rates, etc., which usually have to be addressed before the technical runs can be carried out.

Depending on the progress of the project, the scale-up from kilogram to ton scale in available reactors is then carried out in stages. The kilogram quantities usually are used for certification of the product, and the data from the runs are used to optimize the models for the technical runs.

To scale-up quickly and safely, the support of specialized safety and analytical departments is necessary. Experience with handling highly air-sensitive and expensive homogeneous catalysts is advantageous. Our experience is, that the larger the scale, the easier this is—when one has the appropriate infrastructure and equipment in place.

Irrespective of whether a sample comes out of a batch or continuous process, we have to prepare samples representative of the product quality achievable in the technical process. To do this, we need the support of specialized groups for unit operations such as distillation or crystallization. Distillations are done, for example, in a distillation laboratory under conditions that can be scaled up. The same holds for preparation of solids.

We would like to discuss some representative projects to illustrate the points made above. Unfortunately, it is not possible to give a large amount of chemical or technical detail due to commercial confidentiality. However, we believe that the workflows as well as the scope and nature of the projects will still be evident.

The first project involved the synthesis of optically active 2-methylpentan-1-ol ("R-methylpentanol") **171**.[155] A number of alternative syntheses of this material have previously been described.[156] Unfortunately, these processes are not well suited for industrial use, due to high costs caused by expensive starting materials, too many synthesis steps, poor yields, or very high purification effort.

A route based on asymmetric hydrogenation therefore appeared attractive to us. Among other things, 2-methylpent-2-enal **176**, a possible starting material based on propionaldehyde, was available within the BASF. Such small molecules, without aromatic groups or a large amount of steric differentiation are not particularly "preferred" substrates. Two different routes were considered. One involved the enantio-

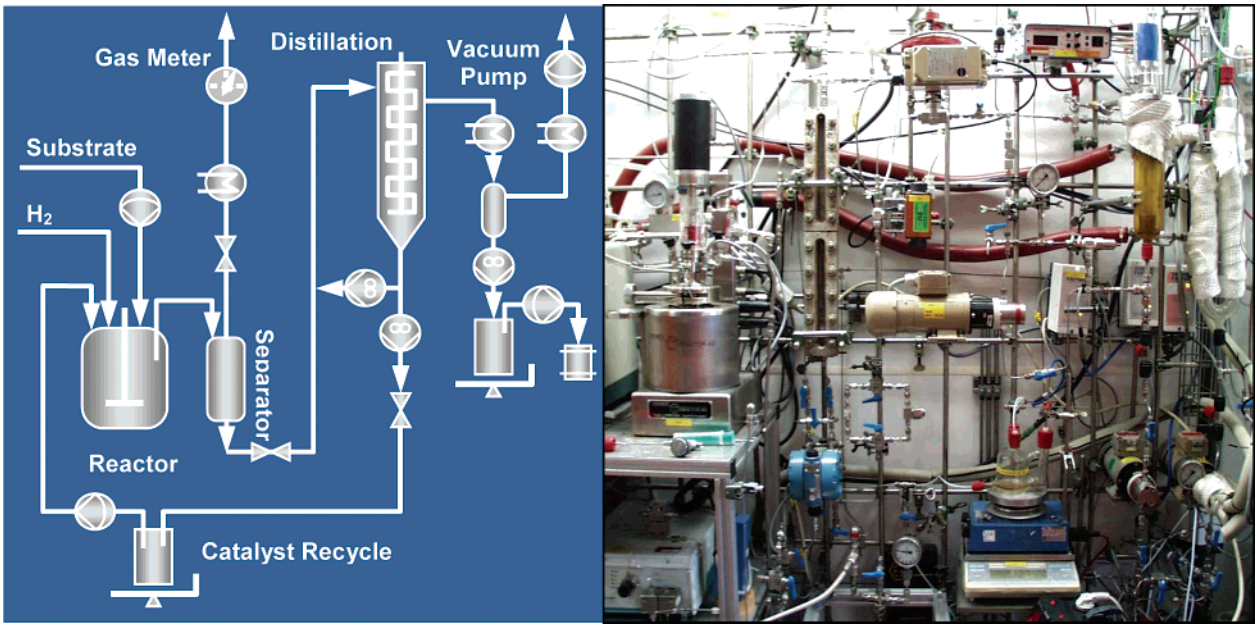
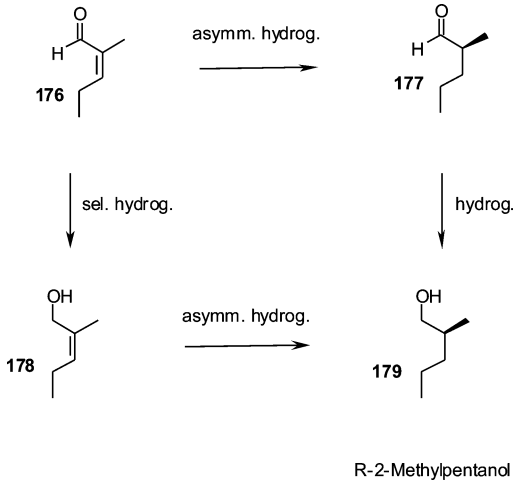


Figure 9. Simple laboratory plant for continuous processing.

Scheme 34. Alternative Routes to R-2-Methylpentanol



selective hydrogenation of the unsaturated aldehyde **176** to the chiral, saturated aldehyde **177**, which could then be further hydrogenated to the desired saturated alcohol **179**. Another involved the chemoselective reduction of the unsaturated aldehyde **176** to the allyl alcohol **178**, followed by an enantioselective hydrogenation to the end product **179** (Scheme 34).

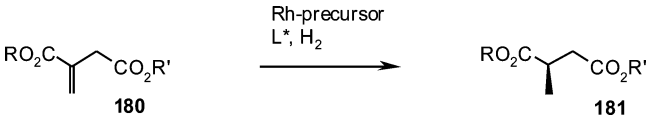
Catalyst identification involved the following steps: set up of high-throughput GC analysis for conversion and ee determination and parallel screening in the Accelerator, involving (i) 16 preselected ligands, two different metals, and two alternative substrates studied in 352 independent reactions (double and control experiments not included) and (ii) variation of reaction parameters with respect to solvent, H_2 pressure, and temperature.

The data indicated that the route via the allylic alcohol using a ruthenium catalyst and a class of privileged ligands had a higher chance of success. The value seen in the first screens, ca. 40% ee, was not very impressive. However, we were able to quickly make the allylic alcohol in large quantities using a heterogeneous catalyst and know-how from another specialized group in our research department. We were then able to optimize the selectivity up to ca. 75% ee in metal autoclaves using pressures not usually considered in this type of chemistry (200 bar, ca. 3000 psi).

At this point, the strength of the BASF research "Verbund" becomes even more apparent. Because of it, we were able to use this product as the feed for an enzymatic resolution using a lipase. The direct resolution of the racemate is not economically feasible. With the enriched feed, however, high optical purity (98% ee) could be achieved at a reasonable price (Scheme 35). The decision was made to scale-up to the technical level. The first runs (asym. hydrogenation stage) in a 3 m^3 reactor at 200 bar ran without any difficulties.

The second project involved a more straightforward problem for the enantioselective hydrogenation, as we wished to synthesize a succinic acid derivative **181** based on an itaconate precursor **180**[157] (Scheme 36). The hydrogenation

Scheme 36. Synthesis of Itaconic Acid Derivatives



of itaconic acid derivatives has often been looked at in the literature, and many catalysts have been reported that yield the desired products with excellent enantioselectivities. However, among those catalysts, we had to find one that would be able to hydrogenate our specific substrate with the desired selectivity. Other important factors for us included patent issues, catalyst cost, and catalyst activity. Despite the large amount of literature for itaconates in general, many of the processes reported for specific derivatives do not deliver ee's sufficient to meet the standards for active pharmaceutical ingredients, usually 98%.[158] Additional steps to enrich the ee would be necessary, with a concomitant increase in costs. Processes capable of yielding higher ee's with such derivatives[159] have often required high catalyst loadings (economically unfeasible) or called for undesirable reaction conditions. The use of the wrong types of solvents, in particular, can cause environmental difficulties or problems concerning worker safety.

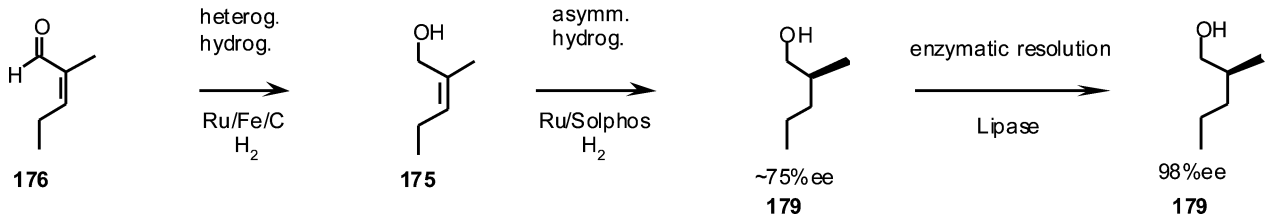
For these reasons, we thought that there would still be a benefit in developing a single-step process for optically active succinic acid derivatives, starting from cheap, easily available materials. The workflow was carried out in a manner similar to that discussed previously. Catalyst identification involved the following steps: set up of high-throughput GC analysis for conversion and ee determination and parallel screening in the Accelerator involving (i) 17 preselected ligands studied in 368 independent reactions (five runs, double and control experiments not included) and (ii) variation of reaction parameters with respect to solvent (MeOH, CH_2Cl_2, toluene), H_2 pressure (3, 5, 10, 20 bar), and temperature (25, 35, 45 °C). We were able to identify a privileged ligand capable of working optimally in our technical reactors.

In the next phase, we optimized the reaction protocol. We transferred to 50 mL-glass autoclaves and achieved full conversion and ≥98% ee at s/c = 100 000/1). We then entered the scale-up phase and started probing the robustness of the reaction protocol under technical conditions in metal autoclaves to guarantee reproducibility. At this stage, we achieved full conversion and ≥98% ee at s/c = 200 000/1).

We then scaled up into a technical reactor without any difficulties. The production runs in a 1 m^3 reactor at 5 bar (75 psi), however, were not done at extremely low catalyst loadings. Very high substrate-to-catalyst ratios may be attractive from a catalyst cost point of view; however, they lead to very long reaction times and production runs of prohibitive length.

The reactions carried out above were both batch reactions. One advantage to having existing equipment and know how

Scheme 35. Final Route to R-2-Methylpentanol



is that one can also test options that are often not considered for pharma projects. For example, we have a small laboratory scale pilot plant, where products can be vacuum distilled away from a catalyst containing high boiler stream (Figure 9). This stream is then returned to the reactor with fresh substrate. This process concept can be easily scaled up for catalyst systems with the necessary thermal stability. Every recycle increases the number of turnovers and reduces the catalyst cost contribution in the product correspondingly.

This type of equipment can be used to look at catalytic cycles quite carefully. And, if the catalyst recycle concept shown works, we have miniplants available where we can make representative 100 kg samples. These are basically scaled up versions of the laboratory unit shown above, which are run by shift workers 24 hours a day, 7 days a week. The scale-up to a small production plant (1−2 t/d) is also possible. Once again, the use of existing equipment offers the opportunity to significantly reduce costs.

7. Summary

Asymmetric hydrogenation has been the subject of interest for many researchers in academia and industry. In fact, directly from the start, this technology was developed to maturity "on both sides of the border" and has triggered the development of many other enantioselective catalytic transformations. From this point of view, asymmetric hydrogenation has always been special. From an industrial point of view, this will remain so in the future. In the last few years, we have seen the deep implementation of asymmetric hydrogenation in the chemical and pharmaceutical industry, with many companies building screening resources and developing their own proprietary catalysts. However, even if companies do not invest heavily in the development of proprietary chiral ligands, one has access today to large ligand libraries deliverable in commercial quantities from technology companies and—for research purposes—from the catalog firms. In this environment, having access to the ligand yielding the highest selectivity is not necessarily decisive anymore. Issues such as development time, catalyst activity, or process intensification are now at least as important as selectivity and determine the cost-effectiveness of a given process. In this regard, process chemists have started to see asymmetric hydrogenation as not being that exotic and strive to design the best process solution for the given commercial environment. Having this in mind, one has to expect much in this field in the coming years.

8. Acknowledgment

BASF AG is greatly acknowledged for the constant support of our work. F. Hettche, J. Rudolph, B. Ostersehlt, and H. Althöfer are acknowledged for the fruitful discussions and many helpful remarks.

9. References

(1) (a) *Combinatorial Chemistry*; Jung, G., Ed.; Wiley-VCH: Weinheim, Germany, 1999. (b) *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, Germany, 2002.
(2) Yue, T.-Y.; Nugent, W. A. *J. Am. Chem. Soc.* **2002**, *124*, 13692.
(3) Boulton, L. T.; Lennon, I. C.; McCague, R. *Org. Biomol. Chem.* **2003**, *1*, 1094.
(4) (a) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 5.1. (b) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 6.1. (c) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Catalysis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 1. (d) Noyori, R. *Angew. Chem.* **2002**, *114*, 2108; *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (e) Knowles, W. S. *Angew. Chem.* **2002**, *114*, 2096; *Angew. Chem., Int. Ed.* **2002**, *41*, 1998. (f) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
(5) (a) *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) Lennon, I. C.; Pilkington, C. J. *Synthesis* **2003**, 1639. (c) Lennon, I. C.; Moran, P. H. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 855. (d) Blaser, H. U.; Benoit, P.; Spindler, F. *J. Mol. Catal. A* **2005**, *231*, 1. (e) Chen, B.; Dingerdissen, U.; Krauter, J. G. E.; Lansink Rotgerink, H. G. J.; Möbus, K.; Ostgard, D. J.; Panster, P.; Riermeier, T. H.; Seebald, S.; Tacke, T.; Trauthwein, H. *Appl. Catal. A* **2005**, *280*, 17. (f) Lida, T.; Mase, T. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 834. (g) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Hendrickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308. (h) de Vries, J. G.; de Vries, A. H. M. *Eur. J. Org. Chem.* **2003**, 799.
(6) Chapter 30: Eckert, M.; Notheis, U. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, J., Eds.; Wiley-VCh: Weinheim, Germany, 2002; p 831.
(7) For a recent review, see: Blackmond, D. G. *Angew. Chem.* **2005**, *117*, 4374; *Angew. Chem., Int. Ed.* **2005**, *44*, 4302.
(8) (a) Gennari, C.; Piarulli, U. *Chem. Rev.* **2003**, *103*, 3071. (b) Archibald, B.; Brümmer, O.; Devenney, M.; Gorer, S.; Jandeleit, B.; Uno, T.; Weinberg, W. H.; Weskamp, T. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, J., Eds.; Wiley-VCh: Weinheim, Germany, 2002; Chapter 32, p 855.
(9) Pugin, B.; Landert, H.; Spindler, F.; Blaser H.-U. *Adv. Synth. Catal.* **2002**, *344*, 974.
(10) Doherty, S.; Robins, E. G.; Pál, I.; Newman, C. R.; Hardacre, C.; Rooney, D.; Mooney, D. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1517.
(11) Augustine, R. L.; Goel, P.; Mahata, N.; Reyes, C.; Tanielyan, S. K. *J. Mol. Catal. A: Chem.* **2004**, *216*, 189.
(12) Gilbertson, S. R.; Wang, X. *Tetrahedron Lett.* **1996**, *37*, 6475.
(13) Gilbertson, S. R.; Wang, X. *Tetrahedron* **1999**, *55*, 11609.
(14) (a) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755. (b) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779.
(15) For the application of dipeptide-based ligands in asymmetric transfer hydrogenation, see: (a) Bogevig, A.; Pastor, I. M.; Adolfsson, H. *Chem.—Eur. J.* **2004**, *10*, 294. (b) Pastor, I. M.; Vastila, P.; Adolfsson, H. *Chem.—Eur. J.* **2003**, *9*, 4031.
(16) Reetz, M. T.; Mehler, G. *Angew. Chem.* **2000**, *112*, 4047; *Angew. Chem., Int. Ed.* **2000**, *39*, 3889.
(17) (a) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961. (b) Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333.
(18) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539.
(19) (a) Komarov, I. V.; Börner, A. *Angew. Chem.* **2001**, *113*, 1237; *Angew. Chem., Int. Ed.* **2001**, *40*, 1197. (b) Guo, H.; Ding, K.; Dai, L. *Chin. Sci. Bull.* **2004**, *49*, 2003.
(20) (a) Ostermeier, M.; Priess, J.; Helmchen, G. *Angew. Chem.* **2002**, *114*, 625; *Angew. Chem., Int. Ed.* **2002**, *41*, 612. (b) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem.* **2002**, *114*, 2454; *Angew. Chem., Int. Ed.* **2002**, *41*, 2348. (c) Chi, Y.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 4849. (d) Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2101. (e) Pakulski, Z.; Demchuk, O. M.; Frelek, J.; Luboradzki, K. M.; Pietrusiewicz, K. M. *Eur. J. Org. Chem.* **2004**, 3913. (f) Junge, K.; Hagemann, B.; Enthaler, S.; Oehme, G.; Michalik, M.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Angew. Chem.* **2004**, *116*, 5176; *Angew. Chem., Int. Ed.* **2004**, *43*, 5066.
(21) Peña, D.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 475.
(22) Reetz, M. T.; Meiswinkel, A.; Mehler, G.; Angermund, K.; Graf, M.; Thiel, W.; Mynott, R.; Blackmond, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 10305.
(23) Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G. *Org. Lett.* **2004**, *6*, 1733.
(24) Liu, Y.; Ding, K. *J. Am. Chem. Soc.* **2005**, *127*, 10488.
(25) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem.* **2003**, *115*, 814.; *Angew. Chem., Int. Ed.* **2003**, *42*, 790.
(26) Peña, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1087.
(27) Reetz, M. T.; Li, X. *Tetrahedron* **2004**, *60*, 9709.
(28) Reetz, M. T.; Mehler, G. *Tetrahedron. Lett.* **2003**, *44*, 4593.

(29) Reetz, M. T.; Li, X. *Angew. Chem.* **2005**, *117*, 3019; *Angew. Chem., Int. Ed.* **2005**, *44*, 2959.

(30) (a) Gao, X.; Kagan, H. B. *Chirality* **1998**, *10*, 120. (b) Brouwer, A. J.; van der Linden, H. J.; Liskamp, R. M. B. *J. Org. Chem.* **2000**, *65*, 1750. (c) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773. For a review, see (d) Satyanarayana, T.; Kagan, H. B. *Adv. Synth. Catal.* **2005**, *347*, 737. For a similar approach for asymmetric hydroformylation, see: Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T. *Org. Lett.* **2004**, *6*, 3277.

(31) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

(32) Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; de Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943.

(33) Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561.

(34) Monti, C.; Gennari, C.; Piarulli, U. *Tetrahedron Lett.* **2004**, *45*, 6859.

(35) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 8737.

(36) Xu, Y.; Alcock, N. W.; Clarkson, G. J.; Docherty, G.; Woodward, G.; Wills, M. *Org. Lett.* **2004**, *6*, 4105.

(37) For a review, see: Noyori, R.; Ohkuma, T. *Angew. Chem.* **2001**, *113*, 40; *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

(38) http://www.umetrics.com/software_modde6.asp (Nov 2005).

(39) Reetz, M. T.; Goossen, L. J.; Meiswinkel, A.; Paetzold, J.; Jensen, J. F. *Org. Lett.* **2003**, *5*, 3099.

(40) (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 1. (b) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (c) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357. (d) Le Gendre, P.; Braun, T.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1996**, *61*, 8453. (e) Jiang, Q.; Xiao, D.; Zhang. Z.; Cao, P.; Zhang, X. *Angew. Chem.* **1999**, *111*, 578; *Angew. Chem., Int. Ed.* **1999**, *38*, 516. (f) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489. (g) Chi, Y.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 4849. (h) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. *Org. Lett.* **2002**, *4*, 4495. (i) Tang, W.; Liu, D.; Zhang, X. *Org. Lett.* **2003**, *5*, 205.

(41) Panella, L.; Feringa, B. L.; de Vries, J. G.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 4177.

(42) (a) Breit, B. *Angew. Chem.* **2005**, *117*, 6976; *Angew. Chem., Int. Ed.* **2005**, *44*, 6916. (b) Wilkinson, M. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Org. Biomol. Chem.* **2005**, *3*, 2371.

(43) (a) Breit, B.; Seiche, W. *J. Am. Chem. Soc.* **2003**, *125*, 6608. (b) Breit, B.; Seiche, W. *Angew. Chem.* **2005**, *117*, 1666; *Angew. Chem., Int. Ed.* **2005**, *44*, 1640.

(44) (a) Weis, M.; Waloch, C.; Seiche, W.; Breit, B. *J. Am. Chem. Soc.* **2006**, *128*, 4188. (b) Jäkel, C.; Volland, M.; Mackewitz, T.; Paciello, R.; Breit, B.; Seiche, W.; Weis, M.; Waloch, C. World Patent Application WO 05/051964, 2005.

(45) (a) Slagt, V. F.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Commun.* **2003**, 2474. (b) Takacs, J. M.; Reddy, D. S.; Moteki, S. A.; Wu, D.; Palencia, H. *J. Am. Chem. Soc.* **2004**, *126*, 4494. (c) Takacs, J. M.; Chaiseeda, K.; Moteki, S. A.; Reddy, D. S.; Wu, D.; Chandra, K. *Pure Appl. Chem.* **2006**, *78*, 501. (d) Jiang, X.-B.; Lefort, L.; Goudrinaan, P. E.; de Vries, A. H. M.; van Leeuwen, P. W. N. M.; de Vries, J. G.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 1223.

(46) (a) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801. (b) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

(47) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.

(48) (a) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062. (b) Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421.

(49) (a) Crepy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79. (b) Cannarsa, M. J. *Specialty Chem. Mag.* **2005**, *25* (4), 42.

(50) (a) Beller, M.; Junge, K.; Monsees, A.; Riermeier, T.; Trauthwein, H. World Patent Application WO 03/033510, 2003. (b) Meseguer, B.; Prinz, T.; Scholz, U.; Militzer, H.-C.; Driessen-Hölscher, B. European Patent EP 1298136, 2003.

(51) For some Binap analogues, see: (a) Miyashita, A.; Karino, H.; Shimamura, J.; Chiba, T.; Nagano, K.; Nohira, H.; Takaya, H. *Chem. Lett.* **1989**, *10*, 1849. (b) Schmid, R.; Cereghetti, M.; Heiser, B.; Schoenholzer, P.; Hansen, H. J. *Helv. Chim. Acta* **1988**, *71*, 897. (c) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370. (d) Yamamoto, N.; Murata, M.; Morimoto, T.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 1085. (e) Murata, M.; Morimoto, T.; Achiwa, K. *Synlett* **1991**, *11*, 827. (f) Yoshikawa, K.; Yamamoto, N.; Murata, M.; Awano, K.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1992**, *3*, 13. (g) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 7283. (h) Enev, V.; Ewers, C. L. J.; Harre, M.; Nickisch, K.; Mohr, J. T. *J. Org. Chem.* **1997**, *62*, 7092. (i) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223. (j) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron Lett.* **2003**, *44*, 823. (k) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264. (l) Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C.; Wong, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 11513. (m) Laue, C.; Schroeder, G.; Arlt, D. European Patent EP 749973, 1996. (n) Gelpke, A. E. S.; Kooijman, H.; Spek, A. L.; Hiemstra, H. *Chem.—Eur. J.* **1999**, *5*, 2472. (o) Henschke, J. P.; Burk, M. J.; Malan, C. G.; Herzberg, D.; Peterson, J. A.; Wildsmith, A. J.; Cobley, C. J.; Casy, G. *Adv. Synth. Catal.* **2003**, *345*, 300. (p) Tang, W.; Chi, Y.; Zhang, X. *Org. Lett.* **2002**, *4*, 1695. (q) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 2043. (r) Bulliard, M.; Laboue, B.; Roussiasse, S. World Patent WO 2002/012253, 2002. (s) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Angew. Chem.* **2004**, *116*, 324; *Angew. Chem., Int. Ed.* **2004**, *43*, 320. (t) Michaud, G.; Bulliard, M.; Ricard, L.; Genêt, J.-P.; Marinetti, A. *Chem.—Eur. J.* **2002**, *8*, 3327.

(52) (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. (b) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934.

(53) (a) Gridnev, I. D.; Yasutake, M.; Imamoto, T.; Beletskaya, I. P. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5385. (b) Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.* **2004**, *37*, 633.

(54) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966.

(55) Liu, D.; Zhang. X. *Eur. J. Org. Chem.* **2005**, 646.

(56) (a) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem.* **1998**, *63*, 8031. (b) Berens, U. World Patent Application WO 2003031456, 2003.

(57) (a) Riermeier, T. H.; Monsees, A.; Almena P.; Juan J.; Kadyrov, R.; Gotov, B.; Zeiss, W.; Nagl, I.; Börner, A.; Holz, J.; Drauz, K.; Meichelboeck, W. World Patent Application WO 2005049629, 2005. (b) Almena, J.; Monsees, A.; Kadyrov, R.; Riermeier, T. H.; Gotov, B.; Holz, J.; Börner, A. *Adv. Synth. Catal.* **2004**, *346*, 1263. (c) Riermeier, T. H.; Monsees, A.; Holz, J.; Börner, A. *Chim. Oggi* **2004**, Suppl. 22. (d) Börner, A.; Holz, J.; Monsees, A.; Riermeier, T. H.; Kadyrov, R.; Schneider, C. A.; Dingerdissen, U.; Drauz, K. World Patent Application WO 2003084971, 2003. (e) Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Börner, A. *J. Org. Chem.* **2003**, *68*, 1701.

(58) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489.

(59) (a) Almena, J.; Monsees, A.; Riermeier, T. H.; Kadyrov, R. *Chim. Oggi* **2005**, *23* (3), 48. (b) Kadyrov, R.; Ilaldinov, I. Z.; Almena, J.; Monsees, A.; Riermeier, T. H. *Tetrahedron Lett.* **2005**, *46*, 7397. (c) Kadyrov, R.; Almena P., Juan J.; Monsees, A.; Riermeier, T. H.; Iladinov, I. European Patent EP 1595888, 2005.

(60) Le, J. C.-D.; Pagenkopf, B. L. *J. Org. Chem.* **2004**, *69*, 4177.

(61) The asymmetric hydrogenation of α-arylenamides with MOM-protected β-hydroxy groups has been reported: Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100.

(62) (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (b) Butsugan, Y.; Ariki, S.; Watanabe, M. *Ferrocenes*; VCH: Weinheim, Germany, 1995; p 143. (c) Takehara, J.; Hashiguichi, S.; Fujii, A.; Inoue, S.-I.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1996**, 233. (d) Peper, V.; Martens, J. *Chem. Ber.* **1996**, *129*, 691.

(63) (a) Sawayama, T.; Tsukamoto, M.; Sasagawa, T.; Naruto, S.; Matsumoto, J.; Uno, H. *Chem. Pharm. Bull.* **1989**, *37*, 1383. (b) Kawai, M.; Omori, Y.; Yamamura, H.; Butsugan, Y. *Tetrahedron: Asymmetry* **1992**, *3*, 1019.

(64) (a) Evans, D. A. *Tetrahedron* **1999**, *55*, 8589. (b) Meyers, A. I. *J. Org. Chem.* **2005**, *70*, 6137.

(65) (a) Roemer, D.; Buescher, H. H.; Hill, R. C.; Pless, J.; Bauer, W.; Cardinaux, F.; Closse, A.; Hauser, D.; Huguenin, R. *Nature* **1977**, *268*, 547. (b) TenBrink, R. E. *J. Org. Chem.* **1987**, *52*, 418. (c) Fincham, C. I.; Higginbottom, M.; Hill, D. R.; Horwell, D. C.; O'Toole, J. C.; Ratcliffe, G. S.; Rees, D. C.; Robert, E. *J. Med. Chem.* **1992**, *35*, 1472. (d) Wu, S. Y.; Takeya, R.; Eto, M.; Tomizawa, C. *J. Pestic. Sci.* **1987**, *12*, 221.

(66) Le, J. C.-D.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 4097.

(67) Maligres, P. E.; Krska, S. W.; Humphrey, G. R. *Org. Lett.* **2004**, *6*, 3147.

(68) (a) Secor, J.; Cseke, C.; Owen, W. J. In *Biocatalysis in Agricultural Biotechnology*; Whitaker, J. R., Sonnet, P. E., Eds.; ACS Symposium Series 389; American Chemical Society: Washington, DC, 1989; p 265. (b) Kikuo, A.; Kiyotaka, Y. Japanese Patent JP 4202168, 1992.

(69) Haskelberg, L. *J. Org. Chem.* **1947**, *12*, 426.

(70) Mathew, N.; Subramanian, S.; Kalyanaasundaram, M. *Ind. J. Chem.* **1996**, *35*, 40.

(71) Joshi, K. C.; Bahel, S. C. *Ind. Chem. Soc.* **1960**, *37*, 365.

(72) (a) Gualtieri, F.; Bottalico, C.; Calandrella, A.; Dei, S.; Giovannoni, M. P.; Maelli, S.; Romanelli, M. N.; Scapecchi, S.; Teodori, E.; Galeotti, N.; Ghelardini, C.; Giotti, A.; Bartolini, A. *J. Med. Chem.* **1994**, *37*, 1712. (b) Amoroso, R.; Bettoni, G.; Tricca, M. L.; Loiodice, F.; Ferorelli, S. *Il Farmaco* **1998**, *53*, 73. (c) Feller, D. R.; Kamanna, V. S.; Newman, H. A. I.; Romstedt, K. J.; Witiak, D. T.; Bettoni, G.; Bryant, S. H.; Conte-Camarino, D.; Loiodice, F.; Tortorella, V. J. *J. Med. Chem.* **1987**, *30*, 1265. (d) Becker, H.; Cassebaum, H.; Leitz, W. *Pharmazie* **1972**, *27*, 411. (e) Redel, J.; Maillard, J. U.S. Patent 2,796,432, 1957.

(73) (a) Perron, Y. G.; Minor, W. F.; Holdrege, C. T.; Gottstein, W. J.; Godfrey, J. C.; Crast, L. B.; Babel, R. B.; Cheney, L. C. *J. Am. Chem. Soc.* **1960**, *82*, 3934. (b) Mejorado, L. H.; Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2004**, *6*, 1535.

(74) The synthesis of related α-hydroxyacids via asymmetric hydrogenation has been described: (a) Zuo, X.; Liu, H.; Guo, G.; Yang, X. *Tetrahedron: Asymmetry* **1999**, *55*, 7787. (b) Wandeler, R.; Kunzle, N.; Schneider, M. S.; Mallat, T.; Baiker, A. *Chem. Commun.* **2001**, 673. (c) Reference 50q.

(75) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D., III; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918.

(76) (a) Direct reduction of α-keto esters towards α-amino acid esters has been reported: Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067. (b) The rhodium-catalyzed asymmetric hydrogenation of benzyl-protected *β*-amino acid esters has been described recently: Dai, Q.; Yang, W.; Zhang, X. *Org. Lett.* **2005**, *7*, 5343.

(77) Ruthenium-catalyzed direct reduction of *β*-keto esters to *β*-amino acid esters has been reported: Matsumura, K.; Saito, T. World Patent Application WO 2005/028419, 2005.

(78) Hansen, K. B.; Rosner, T.; Kubryk, M.; Dormer, P. G.; Armstrong, J. D., III *Org. Lett.* **2005**, *7*, 4935.

(79) Shoop, W. L.; Xiong, Y.; Wiltsie, J.; Woods, A.; Guo, J.; Pivnichny, J. V.; Felcetto, T.; Michael, B. F.; Bansal, A.; Cummings, R. T.; Cunningham, B. R.; Friedlander, A. M.; Douglas, C. M.; Patel, S. B.; Wisniewski, D.; Scapin, G.; Salowe, S. P.; Zaller, D. M.; Chapman, K. T.; Scolnick, E. M.; Schmatz, D. M.; Bartizal, K.; MacCoss, M.; Hermes, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 7958.

(80) Shultz, C. S.; Dreher, S. D.; Ikemoto, N.; Williams, J. M.; Grabowski, E. J. J.; Krska, S. W.; Sun, Y.; Dormer, P. G.; DiMichele, L. *Org. Lett.* **2005**, *7*, 3405.

(81) For the asymmetric hydrogenation of N-sulfonylated indoles, see: Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213.

(82) (a) Sawamura, M.; Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9602. (b) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207. (c) Kuwano, R.; Okuda, S.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 3499. (d) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988. (e) Blaser, H.-U.; Spindler, F.; Studer, M. *Appl. Catal. A* **2001**, *221*, 119. (f) Shieh, W.-C.; Xue, S.; Reel, N.; Wu, R.; Fitt, J.; Repic, O. *Tetrahedron: Asymmetry* **2001**, *12*, 2421. (g) Liu, D.; Li, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4471. (h) Ohashi, A.; Kikuchi, S.-I.; Yasutake, M.; Imamoto, T. *Eur. J. Org. Chem.* **2002**, 2535. (i) Lennon, I. C.; Moran, P. H. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 855. (j) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103.

(83) Chaplin, D.; Harrison, P.; Henschke, J. P.; Lennon, I. C.; Meek, G.; Moran, P.; Pilkington, C. J.; Ramsden, J. A.; Watkins, S.; Zanotti-Gerosa, A. *Org. Process Res. Dev.* **2003**, *7*, 89.

(84) (a) Duggan, M. E.; Naylor-Olsen, A. M.; Anderson, P. A.; Chang, C. T. C.; Cook, J. J.; Gould, R. J.; Ihle, N. C.; Hartman, G. D.; Lynch, J. J.; Lynch, R. J.; Manno, P. D.; Schaffer, L. W.; Smith, R. L. *J. Med. Chem.* **1995**, *38*, 3332. (b) Hipskind, P. A.; Lobb, K. L.; Nixon, J. A.; Britton, T. C.; Bruns, R. F.; Catlow, J.; Dieckman-McGinty, D. K.; Gackenheimer, S. L.; Gitter, B. D.; Iyengar, S.; Schober, D. A.; Simmons, R. M. A.; Swanson, S.; Zarrinmayeh, H.; Zimmermann, D. M.; Dennis, M.; Gehlert, D. R. *J. Med. Chem.* **1997**, *40*, 3721. (c) Plummer, J. S.; Berryman, K. A.; Cai, C.; Cody, W. L.; DiMaio, J.; Doherty, A. M.; Eaton, S.; Edmunds, J. J.; Holland, D. R.; Lafleur, D.; Levesque, S.; Narasimham, L. S.; Rubin, J. R.; Rapundalo, S. T.; Siddiqui, M. A.; Susser, A.; St-Denis, Y.; Winocour, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 835. (d) Duncia, J. V.; Santella, J. B.; Wacker, D. A.; Yao, W.; Zheng, C. World Patent Application WO 01/98268, 2000.

(85) For asymmetric hydrogenations of 2-alkylidenecyclopentanones and -butyrolactones with (Binap)$RuCl_2$, see: Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357. The asymmetric hydrogenation of 3-(4-fluorobenzylidene)valerolactam using (Binap)$RuCl_2$ proceeded with 40% ee: Chung, J. Y. L.; Zhao, D.; Hughes, D. L.; McNamara, J. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7379.

(86) For a recent review on asymmetric hydrogenation of unfunctionalized olefins, see: Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272.

(87) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synt. Catal.* **2003**, *345*, 160.

(88) (a) Lehman, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkinson, W. O.; Willson, T. M.; Kliewer, S. A. *J. Biol. Chem.* **1995**, *270*, 12953. (b) Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leiterdorf, E.; Fruchart, J.-C. *Circulation* **1998**, *98*, 2088.

(89) Houpis, I. N.; Patterson, L. E.; Alt, C. A.; Rizzo, J. R.; Zhang, T. Y.; Haurez, M. *Org. Lett.* **2005**, *7*, 1947.

(90) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966.

(91) For a recent auxiliary-based asymmetric hydrogenation of pyridines, see: (a) Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C. W. *Angew. Chem.* **2004**, *116*, 2910; *Angew. Chem., Int. Ed.* **2004**, *43*, 2850. (b) Scheiper, B.; Glorius, F.; Leitner, A.; Fürstner, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11960.

(92) For other examples of diastereoselective hydrogenation of substituted pyridines, see: (a) Solladié-Cavallo, A.; Marsol, C.; Yaakoub, M.; Azyat, K.; Klein, A.; Roje, M.; Suteu, C.; Freedmann, T. B.; Cao, X.; Nafie, L. A. *J. Org. Chem.* **2003**, *68*, 7308. (b) Douja, N.; Malacea, R.; Banciu, M.; Besson, M.; Pinel, C. *Tetrahedron Lett.* **2003**, *44*, 6991. (c) Douja, N.; Besson, M.; Gallezot, P.; Pinel, C. *J. Mol. Catal. A* **2002**, *186*, 145. (d) Steiner, H.; Giannoussis, P.; Pische-Jaques, A.; Blaser, H.-U. *Top. Catal.* **2000**, *13*, 191.

(93) (a) Lu, S.-M.; Han, X.-Y.; Zhou, Y.-G. *Adv. Synth. Catal.* **2004**, *346*, 909. (b) Wang. W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536.

(94) (a) Raynor, S. A.; Thomas, J. M.; Raja, R.; Johnson, B. F. G.; Belle, R. G.; Mantle, M. D. *Chem. Commun.* **2000**, 1925. (b) Studer, M.; Wedemeyer-Exl, C.; Spindler, F.; Blaser. H.-U. *Monatsh. Chem.* **2000**, *131*, 1335. (c) Blaser, H. U.; Höning, H.; Studer, M.; Wedemeyer-Exl, C. *J. Mol. Catal. A* **1999**, *139*, 253.

(95) Legault, C.; Charette, A. B. *J. Org. Chem.* **2003**, *68*, 7119.

(96) Dorta, R.; Broggini, D.; Kissner, R.; Togni, A. *Chem.—Eur. J.* **2004**, *10*, 4546 and references therein.

(97) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.

(98) James, K.; Alabaster, C. T.; Barclay, P. L.; Barnish, I. T.; Blackburn, K. J.; Brown, D.; Campbell. S. F.; Cussans, N. J.; Danilewicz, J. C.; Palmer, M. J.; Terret, N. K.; Samuels, G. M. R.; Wythes, M. J. *Perspect. Med. Chem.* **1993**, *4*, 45.

(99) (a) Challenger, S. European Patent EP 644176, 1993. (b) Challenger, S.; Derrick, A.; Mason, C. P.; Silk, T. V. *Tetrahedron Lett.* **1999**, *40*, 2187. (c) Burk, M. J.; Bienewald, F.; Challenger, S.; Derrick, A.; Ramsden, J. A. *J. Org. Chem.* **1999**, *64*, 3290. (d) Bulliard, M.; Laboue, B.; Lastennet, J.; Roussiasse, S. *Org. Process Res. Dev.* **2001**, *5*, 438.

(100) Ashcroft, C. P.; Challenger, S.; Derrick, A. M.; Storey, R.; Thomson, N. M. *Org. Process Res. Dev.* **2003**, *7*, 362.

(101) Yuen, P.; Kanter, G. D.; Taylor, C. P.; Vartanian, M. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823.

(102) Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendickson, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L. *Org. Process Res. Dev.* **1997**, *1*, 26.

(103) (a) Burk, M. J.; Goel, O. P.; Hoekstra, M. S.; Mich, T. F.; Mulhern, T. A.; Ramsden, J. A. World Patent Application WO 01/55090, 2001. (b) Burk, M. J.; de Koning, P. D.; Grote, T. M.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Kissel, W. S.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem.* **2003**, *68*, 5731

(104) (a) Hoge, G. *J. Am. Chem. Soc.* **2003**, *125*, 10219. (b) Hoge, G. *J. Am. Chem. Soc.* **2004**, *126*, 9920.

(105) (a) Göschke, R.; Maibaum, J. K.; Schilling, W.; Stutz, S.; Rigollier, P.; Yamaguchi, Y.; Cohen, N.-C. European Patent EP 678503, 1994. (b) Rahuel, J.; Rasetti, V.; Maibaum, J.; Rüeger, H.; Göschke, R.; Cohen, N.-C.; Stutz, S.; Cumin, F.; Fuhrer, W.; Wood, J. M.; Grütter, M. G. *Chem. Biol.* **2000**, *7*, 493. (c) Göschke, R.; Cohen, N.-C.; Wood, J. M.; Maibaum, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2735. (c) Göschke, R.; Stutz, S.; Heinzelmann, W.; Maibaum, J. *Helv. Chim. Acta* **2003**, *86*, 2848.

(106) Herold, P.; Stutz, S. World Patent Application WO 02/02500, 2000.

(107) (a) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries J. G.; Feringa, B. L. *Angew. Chem.* **2005**, *117*, 4281; *Angew. Chem., Int. Ed.* **2005**, *44*, 4209. (b) de Vries, A. H. M.; LeFort, L.; Boogers, J. A. F.; de Vries, J. G.; Ager, D. J. *Chim. Oggi* **2005**, *23* (5), 18.

(108) Miller, W. H.; Alberts, D. P.; Bhatnagar, P. K.; Bondinell, W. E.; Callahan, J. F.; Calvo, R. R.; Cousins, R. D.; Erhard, K. F.; Heerding, D. A.; Keenan, R. M.; Kwon, C.; Manley, P. J.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Uzinskas, I. N.; Venslavsky, J. W.; Yuan, C. C.-K.; Haltiwanger, R. C.; Gowen, M.; Hwang, S.-M.;

James, I. E.; Lark, M. W.; Rieman, D. J.; Stroup, G. B.; Azzarano, L. M.; Salyers, K. L.; Smith, B. R.; Ward, K. W.; Johanson, K. O.; Huffman, W. F. *J. Med. Chem.* **2000**, *43*, 22.
(109) Wallace, M. D.; McGuire, M. A.; Yu, M. S.; Goldfinger, L.; Liu, L.; Dai, W.; Shilcrat, S. *Org. Process Res. Dev.* **2004**, *8*, 738.
(110) (a) Knowles, W. S.; Sabacky, M. J. *Chem Commun.* **1968**, 1445. (b) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.
(111) For example: Burk, M. J.; Feaster, J. E.; Nugent, W. E.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.
(112) Boaz, N. W.; Large, S. E.; Ponasik, J. A., Jr.; Moore, M. K.; Barnette, T.; Nottingham, W. D. *Org. Process Res. Dev.* **2005**, *9*, 472.
(113) Allerton, C. M. N.; Blagg, J.; Bunnage, M. E.; Steele, J. World Patent Application WO 02/014285, 2002.
(114) Appleby, I.; Boulton, L. T.; Cobley, C. J.; Hill, C.; Hughes, M. L.; de Koning, P. D.; Lennon, I. C.; Praquin, C.; Ramsden, J. A.; Samuel, H. J.; Willis, N. *Org. Lett.* **2005**, *7*, 1931.
(115) (a) Devine, P. N.; Hansen, K. B. World Patent Application WO 01/02326, 1999. (b) Hansen, K. B.; Chilenski, J. R.; Desmond, R.; Devine, P. N.; Grabowski, E. J. J.; Heid, R.; Kubryk, M.; Mathre, D. J.; Varsolona, R. *Tetrahedron: Asymmetry* **2003**, *14*, 3581.
(116) (a) Shih, N.-Y.; Shue, H.-J.; Reichard, G. A.; Paliwal, S.; Blythin, D. J.; Piwinski, J. J.; Xiao, D.; Chen, X. World Patent Application WO 01/44200, 2001. (b) Reichard, G. A.; Stengone, C.; Paliwal, S.; Mergelsberg, I.; Majmundar, S.; Wang, C.; Tiberi, R.; McPhail, A. T.; Piwinski, J. J.; Shih, N.-Y. *Org. Lett.* **2003**, *5*, 4249.
(117) For a review, see: Corey, E. J.; Helal, C. J. *Angew. Chem.* **1998**, *110*, 2092; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.
(118) (a) Homann, M. J.; Vail, R. B.; Previte, E.; Tamarez, M.; Morgan, B.; Dodds, D. R.; Zaks, A. *Tetrahedron* **2004**, *60*, 789. (b) Broxterman, Q. B.; Verzijl, G. K. M. World Patent Application WO 03/043575, 2003. (c) Nakamura, K. Japanese Patent JP 2002000284, 2002.
(119) (a) Hansen, K. B.; Devine, P. N. British Patent GB 2351735, 2001. (b) Genov, D. G.; Ager, D. J. *Angew. Chem.* **2004**, *116*, 2876; *Angew. Chem., Int. Ed.* **2004**, *43*, 2816. (c) Ager, D.; Genov, D. G. *Specialty Chem. Mag.* **2004**, *24* (7), 33. (d) Naud, F.; Rüggeberg, C. *Solvias Science Day*, Jan 28, 2005. (e) Naud, F. M.; Pittelkow, U. World Patent Application WO 04/050585, 2002.
(120) For other methods, see hydrosilylation: (a) Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* **2001**, *3*, 4111. Heterogeneous asymmetric hydrogenation: (b) Hess, R.; Krumeich, F.; Mallat, T.; Baiker, A. *J. Mol. Catal. A* **2001**, *212*, 205. (c) Hess, R.; Mallat, T.; Baiker, A. *J. Catal.* **2003**, *218*, 453.
(121) (a) Ikeura, Y.; Doi, T.; Fujishima, A.; Natsugari, H. *Chem. Commun.* **1998**, 2141. (b) Natsugari, H.; Ikeura, Y.; Kamo, I.; Ishimaru, T.; Ishichi, Y.; Fujishima, A.; Tanaka, T.; Kasahara, F.; Kawada, M.; Natsugari, H. *J. Med. Chem.* **1999**, *42*, 3982. (c) Fuji, T.; Ogawa, N. *Tetrahedron Lett.* **1972**, *13*, 3075.
(122) Asymmetric hydrogenation of 2-methylene succinamic acid has been reported, albeit with moderate efficency: Takeda, H.; Tchinami, T.; Hosokawa, S.; Aburatani, M.; Inoguchi, K.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 2706.
(123) Cobley, C. J.; Lennon, I. C.; Praquin, C.; Zanotti-Gerosa, A.; Appell, R. B.; Goralski, C. T.; Sutterer, A. C. *Org. Process Res. Dev.* **2003**, *7*, 407.
(124) (a) Robertson, D. W.; Jones, N. D.; Swartzendruber, J. K.; Yang, K. S.; Wong, D. T. *J. Med. Chem.* **1988**, *31*, 185. (b) Robertson, D. W.; Krishinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412.
(125) For transfer hydrogenation approach, see: Watanabe, M.; Murata, K.; Ikariya, T. *J. Org. Chem.* **2002**, *67*, 1712.
(126) Ratovelomanana-Vidal, V.; Girard, C.; Touati, R.; Tranchier, J. P.; Hassine, B.; B.; Genêt, J. P. *Synth. Catal.* **2003**, *345*, 261.
(127) Hems, W.; Rossen, K.; Reichert, D.; Köhler, K.; Almena Perea, J. J. World Patent Application WO 2004/011452, 2004.
(128) (a) Liu, D.; Gao, W.; Wang, C.; Zhang, X. *Angew. Chem.* **2005**, *117*, 1715; *Angew. Chem., Int. Ed.* **2005**, *44*, 1687. (b) Michel, D.; Mettler, H.; McGarrity, J. World Patent Application WO 2005/080370, 2005.
(129) (a) Benincori, T.; Brenna, E.; Sannicolò, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244. (b) Reference 50q. (c) Benincori, T.; Rizzo, S.; Sannicolò, F. *J. Heterocycl. Chem.* **2002**, *39*, 471.
(130) Benincori, T.; Rizzo, S.; Pilati, T.; Ponti, A.; Sada, M.; Pagliarini, E.; Ratti, S.; Giuseppe, C.; de Farra, L.; Sannicolò, F. *Tetrahedron: Asymmetry* **2004**, *15*, 2289.
(131) (a) Gabelman, A. *Bioprocess Production of Flavor, Fragrance, Colour Ingredients*; Wiley-Interscience, 1994; p 66. (b) Ohloff, G. *Progress in Organic Chemistry*; Springer: Wien, 1978; Vol 35. (c) Mosandl. A.; Günther, C. *J. Agric. Food Chem.* **1989**, *37*, 413.
(132) Cobley, C. J.; Foucher, E.; Lecouve, J.-P.; Lennon, I. C.; Ramsden, J. A.; Thominot, G. *Tetrahedron: Asymmetry* **2003**, *14*, 3431.
(133) (a) Wu, J.; Chen, H.; Kwok, W.; Guo, R.; Zhou, Z.; Yeung, C.; Chan, A. C. S. *J. Org. Chem.* **2002**, *67*, 7908. (b) Wu, J.; Ji, J.-X.; Guo, R.; Yeung, C.-H.; Chan, A. C. S. *Chem.—Eur. J.* **2003**, *9*, 2963.
(134) The use of 1,4-diamines in this kind of hydrogenation has been reported earlier: Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* **2004**, *6*, 2681.
(135) Grasa, G. A.; Zanotti-Gerosa, A.; Medlock, J. A.; Hems, W. P. *Org. Lett.* **2005**, *7*, 1449.
(136) Kim, D.-K.; Kim, G.; Gam, J.; Cho, Y.-B.; Kim, H.-T.; Tai, J.-H.; Kim, K. H.; Hong, W.-S.; Park, J.-G. *J. Med. Chem.* **1994**, *37*, 1471.
(137) Puentener, K.; Scalone, M. U.S. Patent 05/0070714, 2003.
(138) (a) Cereghetti, M.; Foricher, J.; Heiser, B.; Schmid, R. European Patent EP 398132, 1990. (b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schoenholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.
(139) Sortaris, J.-B.; Ritleng, V.; Voelkin, A.; Holuigue, A.; Smail, H.; Barloy, L.; Sirlin, C.; Verzijl, G. K. M.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Pfeffer, M. *Org. Lett.* **2005**, *7*, 1247.
(140) http://www.premex-reactorag.ch/d/spezialloesungen/produkteneuheiten/
(141) http://www.biotage.com/DynPage.aspx?id=23682
(142) http://www.baskervilleautoclaves.co.uk/products_standard.html (Nov. 2005).
(143) Lennon, I. C.; Ramsden, J. A. *Org. Process Res. Devel.* **2005**, *9*, 110.
(144) http://www.symyx.com/page.php?p=000105&page=167&pid=7.54.60.65 (Nov. 2005).
(145) Turner, H. W.; Dales, G. C.; VanErden, L.; van Beek, J. A. M. U.S. Patent 6,306,658, 1998.
(146) http://www.kimble-kontes.com/html/pg-767100.html (Nov. 2005).
(147) Thommen, M.; Blaser, H.-U. *Chim. Oggi* **2003**, Jan-Feb, 27.
(148) The effect of mass transfer problems on enantioselectivty in asymmetric hydrogenations can be quite massive: Sun, Y.; Landau, R. N.; Wang, J.; LeBlond, C.; Blackmond, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 1348.
(149) Angelaud, R.; Zhong, Y.-L.; Maligres, P.; Lee, J.; Askin, D. *J. Org. Chem.* **2005**, *70*, 1949.
(150) Geffroy, D.; Hancock, F.; Hems, W. P.; Zanotti-Gerosa, A. *Chim. Oggi* **2004**, *22* (5), 38.
(151) McGarity, S. F.; Brieden, W.; Fuchs, R.; Mettler, H.-P.; Schmidt, B.; Werbitzky, O. In *Asymmetric Synthesis in Industrial Scale: Challenges, Appoaches, Solutions*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 283.
(152) A large number of ligands and ligand kits are available from catalogue houses such as Strem. The larger quantities necessary for production are then available from the technology providers themselves. At this point, two financial models presently predominate. In one model, the catalyst costs (usually high) are fixed and include all of the necessary intellectual property rights, etc. In the other, the catalyst costs are usually lower; however, royalties for catalyst usage, usually based on revenue, have to be negotiated.
(153) Low-pressure hydroformylation using the well-known rhodium/triphenylphosphine catalyst has proven to be a good method for testing whether a reactor system suffers from mass transfer problems from the gas phase. Easily measured catalyst properties, such as the product linearity in the aldehydes produced, the amount of olefin isomerization, and the hydrogenation rate, are extremely dependent on the carbon monoxide partial pressure in the reaction solution. The effective concentration drops if carbon monoxide is being depleted more quickly than it can be restored by mass transfer, leading to characteristic changes, such as an abnormally high product linearity or increased hydrogenation.
(154) http://www.premex-reactorag.ch/d/anlagenbau/produkte/tischautoklaven/(Nov 2005).
(155) Jäkel, C.; Heydrich, G.; Stürmer, R.; Paciello, R. World Patent Application WO 2006/034812, 2006.
(156) (a) Jermyn, M. A. *Aust. J. Chem.* **1967**, *20*, 2283. This author prepared R-methylpentanol by hydrolyzing the *p*-toluenesulfonate salt of L-valine-(*R*)-2-methyl-pentyl ester. (b) Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212. These authors prepared it via a diastereoselective ester−enolate alkylation of a chiral sultam. (c) Zelle, R. E.; DeNinno, M. P.; Selnick, H. G.; Danishefsky, S. J. *J. Org. Chem.* **1986**, *51*, 5032. These authors prepared it via a diastereoselective imide-enolate-alkylation of a chiral oxazolidinone. (d) Barth, S.; Effenberger, F. *Tetrahedron: Asymmetry* **1993**, *4*, 823. These authors prepared R-methylpentanol from racemic methylpentanol via lipase-catalyzed enantioselective acylation.
(157) Hettche, F.; Jäkel, C.; Friedrich, M.; Paciello, R. World Patent Application WO 06/002999, 2006.
(158) (a) Achiwa, K.; Ohga, Y.; Itaka, Y. *Tetrahedron Lett.* **1978**, 19, 4683, 60% ee in methanol. (b) Christopfel, W. C.; Vineyard, B. D. *J. Am. Chem. Soc.* **1979**, 101, 4406, 55% ee in methanol. (c) Saito, S.; Nakamura, Y.; Morita, Y. *Chem. Pharm. Bull.* **1985**, *33*, 5284, 90% ee in benzene/MeOH (1/4). (d) Kawano, H.; Ishii, Y.; Ikariya, T.;

Saburi, M.; Yoshikawa, S. *Tetrahedron Lett.* **1987**, 28, 1905, 60% ee in toluene/THF. (e) Carmichael, D.; Doucet, H.; Brown, J. M. *Chem. Commun.* **1999**, 261. (f) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1972, 94% ee in methanol. (g) Berens, U.; Burk, M. J.; Gerlach A. World Patent Application WO 00/27855, 2000; 95% ee in methanol. (h) Cobley, C. J.; Lennon, I. C.; McCague, R.; Ramsden, J. A.; Zanotti-Gerosa, A. *Tetrahedron Lett.* **2001**, *42*, 7481, 97.4−98% ee, s/c = 10 000. (i) Pilkington, C. J.; Zanotti-Gerosa, A. *Org. Lett.* **2003**, *5*, 1273, 99% ee, s/c = 100 000.

(159) Ostermeier, M.; Brunner, B.; Korff, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 3453. s/c ratio 200/1 with 97.3% ee in dichloromethane; in $C_6H_5CF_3$ s/c 200/1, 98.3% ee; in dichloroethane 99.3% ee and an s/c ratio of 1000/1.

CR040675A