Combinatorial Libraries of Chiral Ligands for Enantioselective Catalysis

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I. Introduction

The discovery of efficient methods for gaining access to enantiomerically pure compounds in the development of pharmaceuticals, agrochemicals, and flavors has been a substantial challenge for chemists. Among the various ways to produce enantiopure compounds, enantioselective homogeneous catalysis constitutes a very appealing strategy as witnessed by the large number of publications in this field and the award of the Nobel Prize 2001 to Knowles,[1] Noyori,[2] and Sharpless.[3] In this approach, a substoichiometric amount (down to 10^{-3} mol %) of a chiral substance (usually a transition-metal complex obtained from a chiral ligand but also with increasing interest a purely organic molecule) catalyzes the transformation of a prochiral substrate while at the same time dissymmetrically shaping the space around the reaction center, so that one stereochemical path is preferentially followed. The choice of an appropriate chiral ligand is perhaps most crucial, its structure being often the result of knowledge-based intuition or serendipity. In addition, an efficient enantioselective catalytic system is usually obtained after extensive trial-and-error optimization of a number of concurrent factors (ligand structure, metal ion, stoichiometry, solvent, temperature, etc.).

In such a complex scenario, combinatorial methodologies may be seen as a response to the requirement of new, more active, and selective catalysts for organic transformations of interest. The application of combinatorial chemistry to enantioselective homogeneous catalysis has lagged behind its use in other areas (e.g., pharmaceuticals lead discovery and optimization). However, in the past seven years there has been accelerated progress as witnessed by the increase of publications in this field (only 2 in 1995 and about 40 in 2002) and the several recent reviews which have covered this subject (Gennari,[4] Hoveyda,[5,6] Jandeleit,[7,8] Bräse,[9] Reetz,[10,11] Gilbertson,[12] de Vries[13]). An additional important consideration in favor of the creation of libraries of chiral catalysts is in regard to the catalyst scope and applicability. In fact, enzymes are typically substrate-specific, whereas synthetic catalysts usually possess a broader substrate scope. However, there is no general synthetic catalyst, one that is good for every reaction and every substrate. Diversity is important and necessary: a flexible generation of catalyst libraries enhances the chances to find systems with optimum performance (reactivity and selectivity) for different substrates.

A. Asymmetric Catalysis with Chiral Metal Complexes Is Combinatorial in Itself

The active catalyst often self-assembles in the reaction medium along with many other complexes which may have a deleterious or no activity at all, thus giving origin to dynamic combinatorial libraries of different ligand−metal complexes. Two very nice examples of this phenomenon are the Sharpless asymmetric epoxidation and the hydrogenation of enamides by chiral diphosphane rhodium complexes, which are among the few reactions where the mechanistic pathway has been elucidated. In the first case, Sharpless has shown that several titanium tartrate complexes coexist in solution and, in this case, the most abundant dimeric species is also the catalytic active one.[14] In the second case, Halpern[15] and Brown[16] showed that the hydrogenation of enamides in the presence of a C_2-chiral diphosphane Rh complex proceeds by oxidative addition of H_2 to diastereomeric Rh−substrate chelate complexes followed by stepwise transfer of the two hydrides to the coordinated olefin. Most significantly, the minor diastereomer of these complexes is the more reactive one. Another, very interesting example of dynamic combinatorial libraries of different ligand−metal complexes is offered by the so-called NLE's (nonlinear effects).[17] Oguni described this effect for the dieth-

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Cesare Gennari was born in Milan (Italy) in 1952. He graduated in chemistry from Milan University in 1975. After becoming an assistant professor at the same university in 1978 in the group of Professor Scolastico, he joined Professor Clark Still's group at Columbia University as a research associate from 1982 to 1983. In 1985 he became an associate professor at Milan University, and in 1994 he accepted the appointment as Professor of Organic Chemistry at the same university. His awards include a NATO senior fellowship (1985), the Ciamician medal of the organic division of the Italian Chemical Society (1986), the Federchimica prize (1993), and the Karl Ziegler–Giulio Natta award and honorary lecture (Gesellschaft Deutscher Chemiker & Italian Chemical Society, 1997). He is presently a member of the consulting board of editors of *Tetrahedron: Asymmetry* and of *the European Journal of Organic Chemistry*. His research interests include the design and development of new enantioselective methods and their application to the synthesis of natural and unnatural targets with interesting biological and chemical properties. More recently, he has been involved in the synthesis of combinatorial libraries of chiral ligands for enantioselective catalysis.

Umberto Piarulli was born in Varese (Italy) in 1965. He received his Ph.D. degree from the University of Lausanne in 1996 under the supervision of Professor C. Floriani studying carbohydrate–metals coordination chemistry. In 1996 he became Researcher of Organic Chemistry at Milan University (Como branch) in the group of Professor Gennari. Since 1998 he has held the same position at the University of Insubria at Como. His main research interests are enantioselective catalysis, organometallic chemistry, and the synthesis of libraries of chiral ligands.

ylzinc addition to aldehydes catalyzed by chiral, nonenantiopure amino alcohols,[18] and the mechanism was thoroughly investigated by Noyori.[19,20] Accordingly, diethylzinc forms with the two enantiomeric amino alcohol ligands two diastereomeric dimeric structures, a homodimer, where the two amino alcohols have the same configuration, and a heterodimer. It is the less stable homodimer that dissociates and forms the active species in the presence of the aldehyde and excess diethyl zinc, thus allowing high enantioselectivities to be obtained in the reaction even when starting from ligands of much lower enantiomeric excess.[21]

Attempts to take advantage of these concepts combinatorially, through ligand and additive diversity, are discussed in section V (Parallel Libraries Resulting from Combinations of Chiral/Achiral Metal–Ligands and Additives).

In addition, the use of randomly generated mixtures of ligands would seem very appealing. This idea was developed by Menger and co-workers, who produced randomly generated polymers as catalysts for the hydrolysis of a phosphodiester[22] and for the dehydration of a β-hydroxyketone.[23] In both cases, a functionalized polymer is derivatized using various combinations of reagents and the resulting multifunctional polymer is routinely screened for catalytic activity. However, the precise structure of the catalytic polymer remains unknown. Menger states "The structure of most catalytic antibodies is unknown, and the same is true for our combinatorial polymers."[22] This approach (i.e., the function is important, not the structure) might become valuable also in searching for new enantioselective catalysts, as implied in a preliminary report by Bolm[24] and discussed in section VI (Chiral Ligands with Undetermined Structure).

However, at present the most common combinatorial approach to chiral ligands for enantioselective catalysis is based on a modular approach: ligand libraries are synthesized in solution or on a solid support via the coupling of different subunits. We believe that the slow step in such an approach is the preparation of catalyst libraries rather than their screening, so any advance that enables faster production of ligands with good molecular architecture for enantioselective catalysis is important. This contribution will cover the synthesis and screening of libraries of chiral metal–ligands (see section II) and organic catalysts (see section III) possessing a modular structure, both in solution and on the solid phase.

In addition, the high-throughput screening of arrays of metals and chiral ligands will also be reviewed (see section IV).

Our contribution will *not* cover the following:

(a) enzymes and their directed evolution (Reetz,[10,25–28] DeSantis[29]),

(b) the combinatorial optimization of reaction parameters (temperature, pressure, solvent, catalyst loading, etc.), and

(c) approaches to high-throughput ee assays: UV/vis spectroscopy,[30,31] mass spectrometry[32,33] and NMR spectroscopy[34] using isotopically labeled substrates (pseudoenantiomers), mass spectrometry of "mass-tagged" diastereomeric substrates,[35] IR-thermography,[36,37] capillary array electrophoresis,[38] special forms of GC,[39] CD spectroscopy,[40–44] enantioselective fluorescent sensors,[45–48] enantioselective colorimetric sensors,[49] color indication of enantiomeric excess based on doped liquid crystals,[50,51] pH indicators,[52,53] proteins,[54] molecularly imprinted polymers,[55] immunoassays and antibodies,[56] enzymatic methods,[57,58] enantioselective fluorogenic assays,[59] and DNA microarrays.[60] These methodologies will not be reviewed

per se but only when they are used in enantioselective catalysis applications.

II. Libraries of Chiral Metal–Ligands with a Modular Structure (Synthesis and Screening)

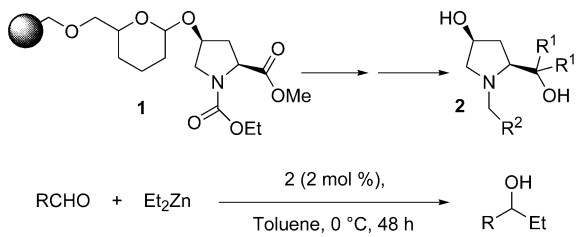
The screen of a library comprising chiral ligands for enantioselective catalysis is ultimately the catalysis of a reaction and the evaluation of its stereochemical outcome (enantiomeric excess). For this reason, parallel synthesis (as opposed to the split and pool methodology) is usually preferred, since it allows the positional identification of each single ligand and keeps the different ligands separate so that individual screening can be performed. In fact, the high-throughput ee screening of split and pool libraries of chiral catalysts is still in its infancy, and the ee screening of a single bead-bound catalyst is at the level of proof of concept.[11]

In this section we illustrate the synthesis of parallel libraries of chiral ligands possessing a modular structure and their screening in enantioselective metal-catalyzed reactions.

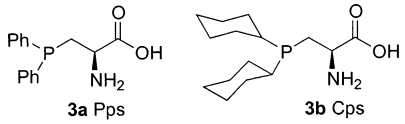
This strategy was first explored by Ellman[61] and co-workers in 1995 with a small library (10 members) of pyrrolidinemethanol ligands **2** (Scheme 1). The ligands were prepared on the solid phase (PS-1%-DVB resin functionalized with a dihydropyran linker) by reaction of resin-bound *N*-[(ethyloxy)carbonyl]-4-hydroxyprolinemethylester **1** with a large excess of seven different Grignard reagents (R^1MgX) and transformation of the *N*-protecting group by reduction to CH_3 or hydrolysis and reductive alkylation. The ligand library was screened in the enantioselective 1,2-addition of diethylzinc to aldehydes. One of the ligands was tested both resin-bound and in solution (after cleavage). The supported ligand gave a somewhat reduced selectivity (89 vs 94% ee), and therefore all the ligands were cleaved from the resin before screening. Enantioselectivities were usually very good (up to 94% ee in favor of the *S* enantiomer). Despite the small size of the library and the limited structural diversity, this pioneering work paved the way to all the subsequent developments.

One of the easiest ways to increase the structural diversity of ligand libraries is to use peptide chemistry, which is well established and highly modular. Several authors have followed this strategy. In 1996 Gilbertson and co-workers reported the parallel synthesis of phosphine ligands, where phosphine-containing amino acids are embedded in peptide secondary structures.[62,63] Two serine derivatives, namely, diphenylphosphino- (Pps, **3a**) and dicyclohexylphosphinoserine (Cps, **3b**), were used to build a 63-member library of deca- and undecapeptides

Scheme 1



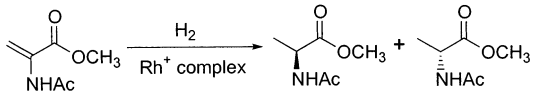
Scheme 2



Structure of the Library

Ac-Ala-Aib-Ala-X^1-AA^1-AA^2-AA^3-X^2-Ala-Aib-Ala-Resin
Ac-Ala-Aib-Ala-X^1-X^2-AA^1-AA^2-AA^3-Ala-Aib-Ala-Resin
Ac-Ala-Aib-Ala-AA^1-AA^2-AA^3-X^1-X^2-Ala-Aib-Ala-Resin
Ac-Ala-Aib-Ala-AA^1-AA^2-X^1-X^2-Ala-Aib-Ala-Resin

AA^1, AA^2, AA^3 = Phe, Val, His, Ile, Ala, Aib
X^1, X^2 = Pps, Cps



Scheme 3

2^{nd} generation library

Ac-Ala-Ala-Aib-Ala-dX^1-Ala-Ala-X^2-AA^1-Ala-Aib-Ala-Resin
Ac-Ala-Ala-Aib-Ala-dX^1-AA^1-Ala-Ala-X^2-Ala-Ala-Aib-Ala-Resin
Ac-Ala-Ala-Aib-Ala-dX^1-Ala-Ala-AA^1-X^2-Ala-Ala-Aib-Ala-Resin

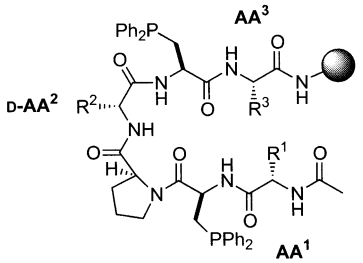
AA^1 = Phe, Val, His, Ile, Ala, Aib
X^1, X^2 = Pps, Cps

(Scheme 2). The library was prepared on the solid phase, on spatially separated multipins. Each member of the library contained the α-helix-inducing sequence Ala-Aib-Ala (Aib = α,α-dimethylglycine) at both termini of the peptide, with the aim of bringing the two phosphines in a suitable spatial arrangement for metal binding. Between these two sequences, a tetra- or pentapeptide was introduced that was varied combinatorially. These two combinatorial sequences contained the two phosphine-bearing serines (X^1, X^2) in either a *i*, *i*+4 disposition (27 members) or positioned next to each other (36 members).

The solid-phase-bound peptide sequences were loaded with rhodium ions by reaction with Rh(NBD)-ClO_4. The Rh-complexed peptide sequences were then screened for hydrogenation of 2-acetamidoacrylate in THF, with poor ee's (≤17%). On the basis of modeling studies, a second-generation library (Scheme 3) was then prepared using a phosphine-containing D-amino acid in the *i* position and a phosphine-containing L-amino acid in the *i*+3 (24 members) or *i*+4 (24 members) positions. Nevertheless, low ee's (≤38%) were still obtained. The best ligand sequences were cleaved from the resin and tested in solution (in DCM, THF, or water): the results in water were comparable to the solid phase, while those in DCM and THF were completely different. This is possibly due to the high hydrophobicity of the peptides studied, which might therefore show some aggregation and tertiary structure in water.

Another 96-member library was prepared on pins, with two Pps residues (**3a**) flanking a β-turn-inducing

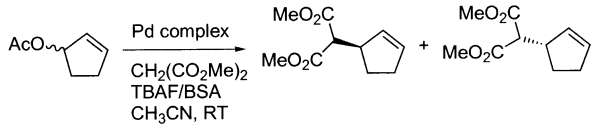
Scheme 4



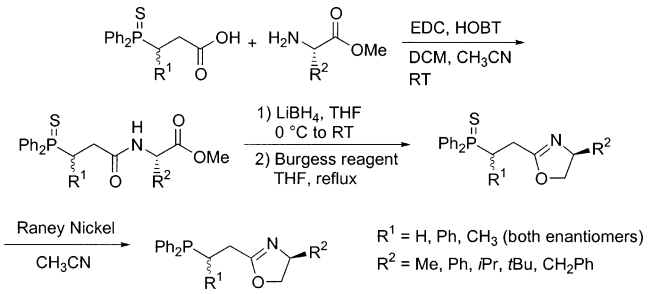
AA1, AA3 = Ala, Gly, Phe, Glu, Cys, Ser, Lys, Tyr, D-Ala, D-Met, D-Phg, D-Val, D-Phe

AA1 only = Phg, His, Trp

D-AA2 = D-Ala, D-Met, D-Phg, D-Val, D-Phe, D-Leu, Gly



Scheme 5

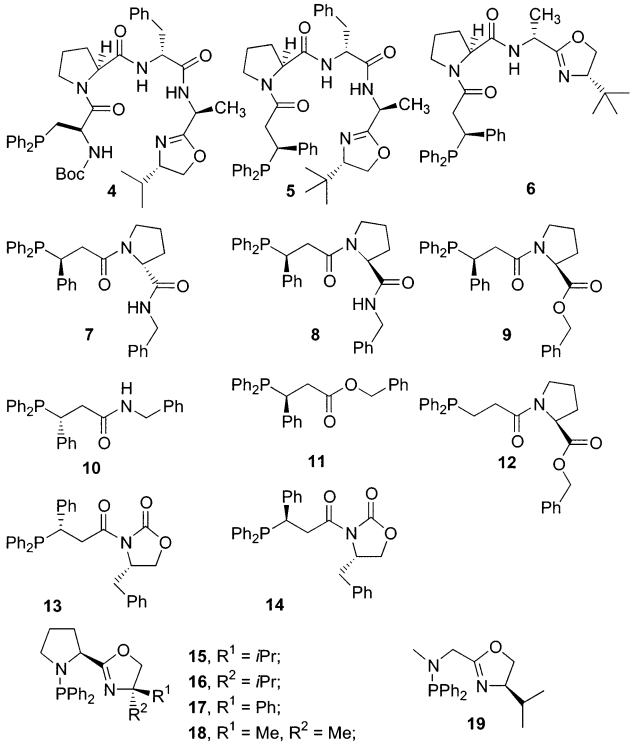


motif (Pro + D-amino acid) and two other amino acids as variable sites (Scheme 4).[64] The library was tested in the allylic addition of dimethyl malonate to cyclopentenyl acetate. The selectivities obtained with this library ranged from 34% to 80% ee.

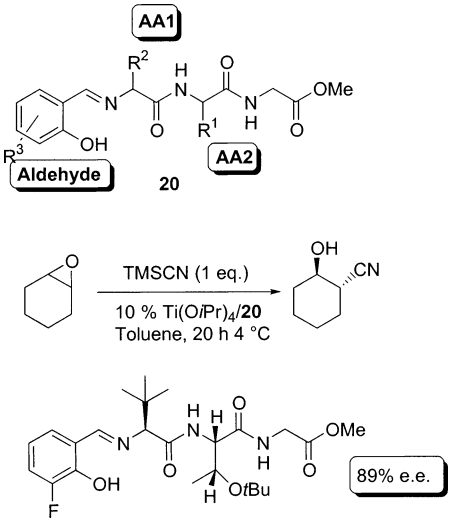
In 1997−98 Gilbertson and co-workers reported a small library of chiral phosphine−oxazoline ligands.[65,66] The library (14 ligands) was obtained via a three-step modular process encompassing coupling of β-diphenylphosphino acids with natural amino acids, selective reduction of the carboxy terminus, and cyclization to the phosphine−oxazoline ligands (Scheme 5). The ligands were screened in the enantioselective allylic substitution of 1,3-diphenylprop-2-enyl acetate and 2-cyclopentenyl acetate with dimethyl malonate. After extensive optimization of the reaction conditions, ligands with two stereogenic centers ($R^1 \neq H$) gave ee's up to 98% and yields up to quantitative in the first case, whereas in the case of 2-cyclopentenyl acetate the results were rather disappointing (ee $\leq$ 42%).

In a similar way, a series of ligands (**4**−**14**, Chart 1) containing the amino acid Pps (**3a**) and a number of β-diphenylphosphino acids, were prepared and tested in the allylic substitution of cyclopentenyl acetate with dimethyl malonate, with enantiomeric excesses up to 88%.[67] Finally, a series of modular P−N ligands (**15**−**19**, Chart 1) were synthesized by reaction of proline (for **15**−**18**) and *N*-methyl glycine (for **19**) with Ph_2PCl, resulting in formation of the P−N bond, followed by transformation of the caboxy-

Chart 1



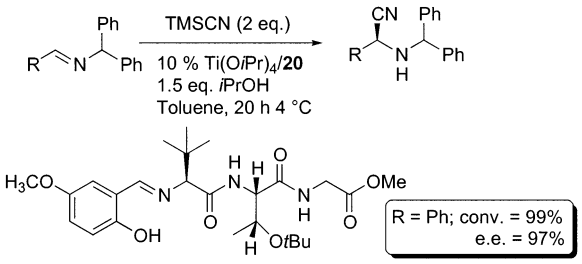
Scheme 6



lic moiety in a chiral oxazoline ring. These ligands proved effective in the Pd-catalyzed allylation of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate (ee up to 94%), benzylamine (ee up to 97%), and phthalimide (ee up to 91%).[68]

A substantially different approach to libraries of peptide-derived ligands was employed by Snapper, Hoveyda, and co-workers who, in 1996, reported the solid-phase synthesis of a library of tripeptide phenolic Schiff bases (**20**, SB-AA1-AA2-GlyOMe, SB = Schiff base, Scheme 6) for the Ti(O*i*Pr)$_4$-mediated ring opening of meso cyclic epoxides (five-, six- and seven-membered ring) with TMSCN.[69] Using 10 amino acids at the AA1 position, 16 amino acids at the AA2 position, and 13 substituted salicylaldehydes, a library of 10 × 16 × 13 = 2080 members could, in principle, be prepared on polystyrene beads. Instead,

Scheme 7

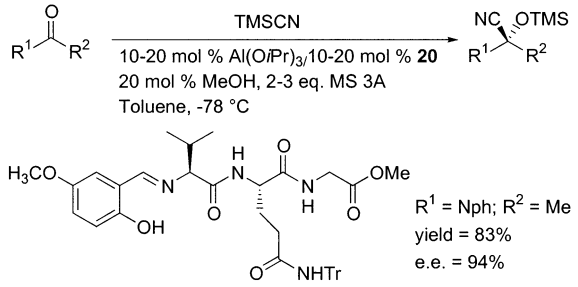


a "positional scanning" approach was followed for ligand optimization, which involves varying one module of the structure (e.g., AA1) while keeping the other modules (SB, AA2) constant, and so on. In this way, the number of ligands required for the optimization is dramatically reduced (10 + 16 + 13 = 39), although this procedure may fail to identify the best absolute ligand, which is guaranteed from the screening of the whole library. In general, the "positional scanning" approach is very time effective but overlooks the mutual influences of the different modules in the fine-tuning of the modular ligand structure. The ligands were synthesized on solid phase and subsequently cleaved into solution (Et_3N, DMF, MeOH, RT, 60 h) for testing. Enantiomeric excesses as high as 89% were obtained in the cyanide addition to cyclohexene oxide.

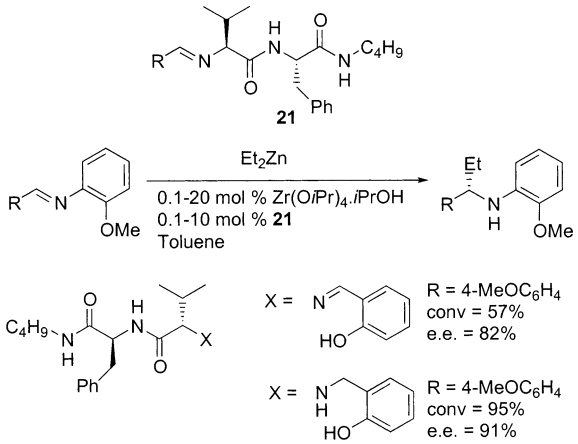
In a subsequent work,[70] the authors addressed the issue of comparing the results using the ligands in solution with the results using the ligands still attached to the solid support. A few members (20) of the library were screened both still attached to the resin and in solution: a linear correlation was found with the best ligand in solution being also the best ligand on the solid phase. In 1999 Snapper, Hoveyda, and co-workers[71] reported the enantioselective cyanide addition to a variety of imines, catalyzed by Ti(O*i*Pr)$_4$/Schiff base **20** (Scheme 7), with excellent enantioselectivities (85−97% ee, by chiral HPLC). After an extensive optimization of the reaction conditions [metal, Ti(O*i*Pr)$_4$; solvent, toluene; imine type, *N*-diphenylmethyl imines; cyanide source, TMSCN], a "positional scanning" optimization was performed (screening of 75 solid-phase-bound ligands and screening of the best ligands also after cleavage into solution), systematically varying the three structural modules of the chiral ligand (SB, AA1, AA2). The reaction efficiency was improved by slow addition of 1.5 equiv of *i*PrOH, which is believed to promote the gradual hydrolysis of TMSCN to HCN. As an extension to this work, the same library of ligands and the same reaction conditions were applied to α,β-unsaturated imines with very good enantioselectivities (76−97% ee) for both aryl- and alkyl-substituted vinyl imines.[72]

A library of 81 tripeptide phenolic Schiff bases (**20**) was also screened in the catalytic, enantioselective cyanide addition to a wide range of aliphatic and aromatic ketones to give tertiary cyanohydrins (Scheme 8).[73] Initial optimization was performed using acetophenone as a model substrate for TMSCN addition: the use of 20 mol % ligand and 20 mol % Al(O*i*Pr)$_3$ (among some 23 different metals tested) was identified as the best reaction conditions. Optimization of the ligand structure was performed with the ligands attached to the solid phase (31 salicylaldehydes, 25 AA1, and 25 AA2) in 1,2-dichloroethane with enantiomeric excesses up to 51% (by chiral GC). Cleavage from the solid phase by methanolysis and testing in solution increased enantiomeric excesses by 15%. Finally, addition of methanol (20 mol %) and 3 equiv of 3-Å molecular sieves gave the best yields and enantioselectivities (up to 94% ee for aromatic ketones and 95% ee for alkenyl, methyl ketones).

Scheme 8

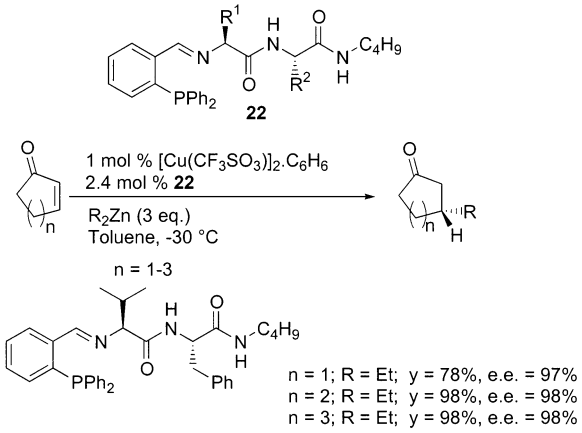


Scheme 9



In a subsequent work, Hoveyda, Snapper, and coworkers reported the solution-phase synthesis of a small library of *dipeptide* imine ligands (**21**) (17 ligands) and its screening in the zirconium-catalyzed enantioselective addition of diethylzinc to imines to give arylamines (Scheme 9).[74] Cu, Ti, B, Zn, Al, and Sc were also tested, but Zr was found to be the most effective. In particular, *N*-*o*-anisidyl imines were alkylated with dialkylzinc reagents in the presence of a zirconium complex of **21** (initially 20% of the complex and then down to 1% of the ligand together with 20% zirconium tetraisopropoxide). Good to excellent enantioselectivities (67−98% ee) were obtained for the addition of diethylzinc to *N*-*o*-anisidyl arylaldimines. Along with the addition product, variable amounts of the reduction product were isolated, which predominated when electron-deficient imines were used. The C=N bond reduction might be due to a metal hydride, which is formed via a rapid β-H elimination of an "EtZr" or "EtZn" complex. This finding suggested that the active chiral ligand may be the derived peptidic amine and not the original Schiff base. Competitive reduction of the highly reactive substrate electron-deficient imine might preclude the in situ generation of the active amine

Scheme 10



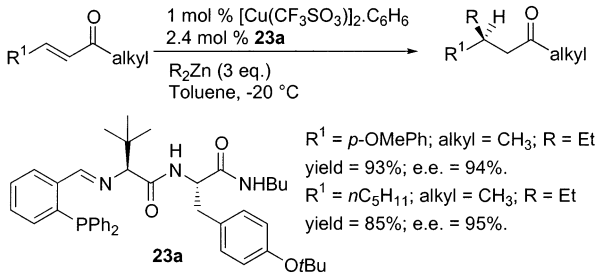
ligand. In fact, when the reduced amine ligands were employed [10 mol % ligand and 11 mol % $Zr(OiPr)_4$·HO*i*Pr] with electron-deficient imines, ethyl addition products were generated efficiently (95% conversion) and in high ee (88−90%). Also in the case of electron-rich imines, higher efficiency (95 vs 57% conversion with the same ligand backbone) and enantioselectivity (91 vs 82% ee) were observed.

Another successful application of peptide Schiff-base ligands was the enantioselective copper-catalyzed conjugate addition of dialkylzinc reagents to enones.[75] However, in this case the phenolic Schiff-base peptide ligands, which proved very effective in a number of enantioselective processes catalyzed by early transition metals, produced almost racemic mixtures (with a variety of solvents and copper sources) when tested in the copper-catalyzed conjugate addition of Et_2Zn to cyclopentenone. 2-(Diphenylphosphino)benzaldehyde was then used, and a ligand library of diphenylphosphine Schiff-base dipeptide derivatives (**22**) was synthesized on a solid support and cleaved into solution for testing. Positional optimization of AA1 (20 amino acids) and AA2 (22 amino acids) was then performed using the copper(I) triflate−benzene complex (1 mol %) in toluene: under these conditions, 3-ethylcyclopentanone (Scheme 10) was obtained with almost complete conversions and excellent enantioselectivities (from 79 to 98% ee). This result is particularly valuable as other ligands are known from the literature to perform well with cyclohexenone and cycloheptenone but not with cyclopentenone.[75] When six- and seven-membered cyclic enones were used, complete conversions to the products with enantiomeric excesses higher than 98% were obtained.

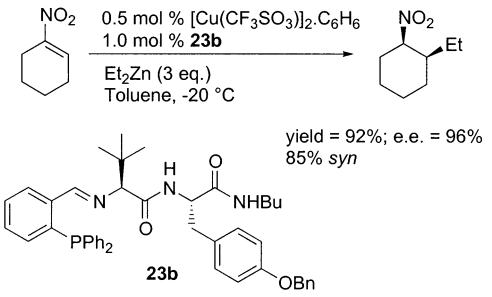
The same library was also screened for the copper-catalyzed asymmetric conjugate addition of dialkylzinc reagents to both aromatic and aliphatic conjugated acyclic ketones (Scheme 11).[76] In both cases, excellent enantioselectivities, ranging from 89% to 95% ee, were obtained with ligand **23a**.

A slightly modified ligand structure (with *O*-benzyl-protected tyrosine in place of *O*-*t*Bu-tyrosine, **23b**) was also tested in the conjugate addition to cyclic nitroolefins (Scheme 12).[77] Good to excellent yields and high diastereo- (syn) and enantioselectivities were obtained for the five- and six-membered rings. Treatment of the cis nitroalkanes with 1 equiv of

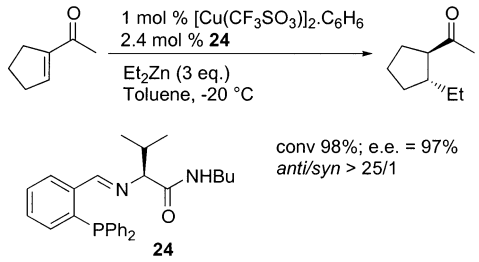
Scheme 11



Scheme 12



Scheme 13

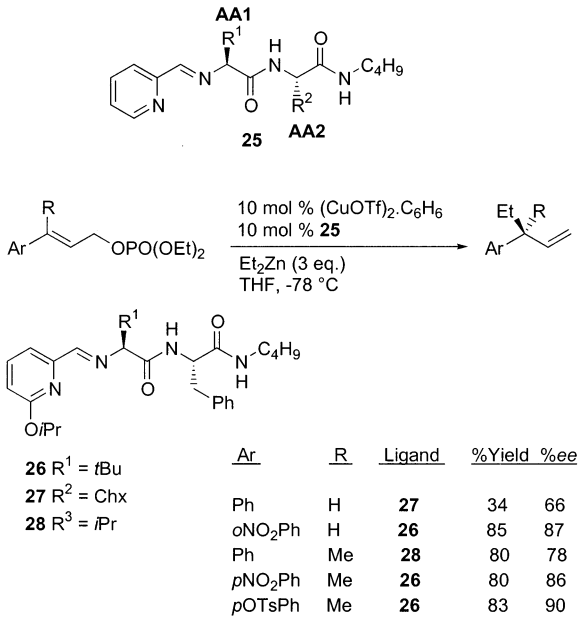


DBU led to the efficient and clean formation of the corresponding trans isomers via epimerization at the stereocenter bearing the nitro group, without a lowering of enantiomeric excess. Conjugate addition of diethylzinc to 1-nitrocycloheptene afforded 2-ethylcycloheptanone (derived from the Nef reaction) in moderate yield and very good ee (93%).

In addition, trisubstituted cyclic enones, such as acetyl-cyclopent-1-ene and related substrates, were also reported to give asymmetric conjugate addition of dialkylzinc reagents. Interestingly, excellent conversions (>90%) to the anti product (*anti:syn* ratios from 16:1 to 25:1) and good to excellent enantioselectivities (73−98% ee) were obtained when a diphenylphosphine Schiff base derivative of a single amino acid (**24**, lacking AA2) was used as ligand (Scheme 13).[78]

A new class of peptide Schiff-base ligands (**25**) containing a pyridine−-carboxaldehyde-derived imine was tested in the Cu-catalyzed allylic alkylation reaction of allylic phosphates using dialkylzinc reagents (Scheme 14).[79] The optimization procedure required four steps: (i) identification of the optimal Schiff-base type (phenol, PPh_2, pyridine), (ii) identification of the most effective Cu salt, (iii) determination of the optimal peptide length (di- vs tripeptide), and (iv) enhancement of the enantioselectivity through a positional optimization of the substituents (18 different amino acids for the AA1 position and 22 amino acids for the AA2 position). At the end of

Scheme 14



Ar	R	Ligand	%Yield	%*ee*
Ph	H	**27**	34	66
oNO_2Ph	H	**26**	85	87
Ph	Me	**28**	80	78
pNO_2Ph	Me	**26**	80	86
*p*OTsPh	Me	**26**	83	90

this procedure, pyridinyl dipeptide ligands **26**, **27**, and **28** were identified, which gave catalytic alkylation of aryl-substituted allylic phosphates in moderate to good enantioselectivities (66−87% ee, R = H, Scheme 14). When trisubstituted olefins (R = Me) were tested, the catalytic enantioselective synthesis of quaternary carbon centers was obtained with enantiomeric excesses ranging from 78% to 90%.

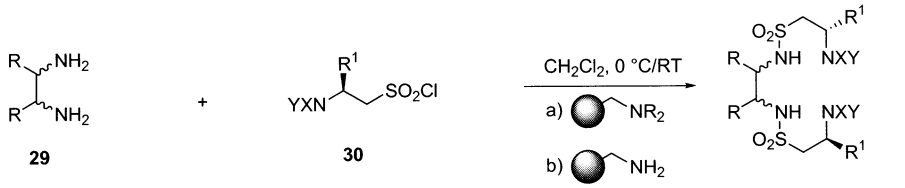
In 1998 Gennari, Piarulli, and co-workers reported the synthesis of a library of modular bis-sulfonamide ligands **31** containing two chiral *N*-Boc-β-amino sulfonamide arms (prepared from natural α-amino acids).[80] A parallel library of 30 ligands (obtained from six diamine scaffolds **29** and five *N*-Boc-β-amino sulfonyl chlorides **30**) was prepared in solution using a resin scavenging technique to avoid chromatographic purification of the ligands (Scheme 15).

These were tested in the enantioselective Et_2Zn addition to aldehydes. An original multisubstrate approach was developed by running the screening reaction on a mixture of four different, aromatic and aliphatic, aldehydes (Scheme 16). The enantioselectivities were measured by chiral GC, and the aldehydes were chosen so that the four pairs of enantiomeric alcohol products gave separate peaks with baseline separation. With the optimal ligand identified via this *high-throughput* screening methodology, excellent enantiomeric ratios were obtained with both aromatic and aliphatic aldehydes in favor of the (*R*)-alcohol [*R:S* = 93:7 (**33l**), 98:2 (**33m**), 98:2 (**33n**), 97:3 (**33o**)]. The best ligand was then synthesized on a preparative scale, purified by chromatography, and fully characterized, and the screening results were confirmed by reaction with the four separate aldehydes.

The multisubstrate approach was independently reported by Kagan and co-workers in 1998 for the asymmetric reduction of mixtures of prochiral ketones using a chiral oxazaborolidine catalyst.[81,82] Small libraries of prochiral ketones (up to seven different substrates) were reduced, and the resulting alcohols were analyzed by chiral HPLC. This methodology should, in principle, allow for the analysis of large mixtures of products arising from prochiral substrates, provided that the products do not interfere with the catalyst (no autoinduction) and the chromatographic peaks do not overlap during the elution. A solid-phase-supported library of bis-sulfonamide ligands (**34**, on Argogel resin) containing two chiral *N*-Boc-β-amino sulfonamide arms was reported in the year 2000 by Liskamp and co-workers using a 3,4-*trans*-diamino pyrrolidine scaffold.[83] The library (10 members: two scaffolds and five *N*-Fmoc-β-amino sulfonyl chlorides) was tested in the enantioselective Et_2Zn addition to aldehydes using the previously described multisubstrate approach[80] on a mixture of four different, aromatic and aliphatic, aldehydes (Scheme 17). Low enantiomeric excesses were obtained (max 32% ee with *S,S* diamine scaffold and R = *i*Bu), which could be improved to a maximum of 66% after cleavage into solution.

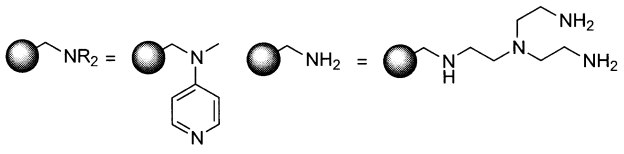
The previously described multisubstrate approach[80] was reported by Wolf and co-workers in 2002 for the enantioselective Et_2Zn addition to aldehydes using *N*-substituted *nor*-ephedrine ligands with moderate to good enantioselectivities (up to 94% ee with benzaldehyde).[84] More recently, Feringa and co-

Scheme 15

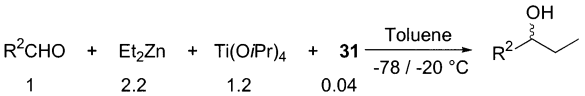


29a R,R = -$(CH_2)_4$- (*R,R*)
29b R,R = -$(CH_2)_4$- (*S,S*)
29c R,R = -$(CH_2)_4$- (*R,S*)
29d R,R = -$(CH_2)_4$- (±)
29e R,R = Ph (*R,R*)
29f R,R = Ph (*S,S*)

30g R^1 = CH_3; X = H; Y = Boc
30h R^1 = $CH(CH_3)_2$; X = H; Y = Boc
30i R^1 = $CH_2CH(CH_3)_2$; X = H; Y = Boc
30j R^1 = CH_2Ph; X = H; Y = Boc
30k R^1,X = -$(CH_2)_3$-; Y = Cbz



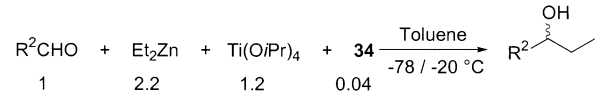
Scheme 16



32l R^2 = Chx
32m R^2 = Ph
32n R^2 = $PhCH_2CH_2$
32o R^2 = $pClC_6H_4$

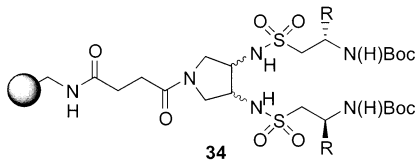
33l R^2 = Chx
33m R^2 = Ph
33n R^2 = $PhCH_2CH_2$
33o R^2 = $pClC_6H_4$

Scheme 17



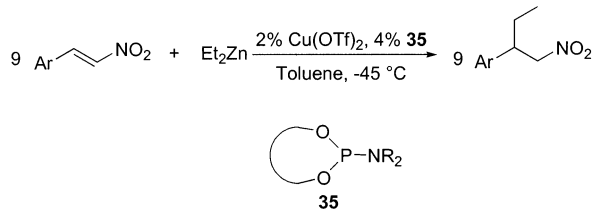
32l R^2 = Chx
32m R^2 = Ph
32o R^2 = $pClC_6H_4$
32p R^2 = $PhCH_2$

33l R^2 = Chx
33m R^2 = Ph
33o R^2 = $pClC_6H_4$
33p R^2 = $PhCH_2$



34

Scheme 18



35

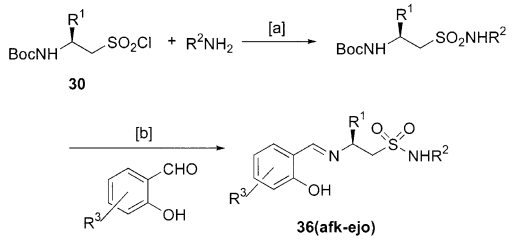
(8 different chiral phosphoramidite ligands)

workers[85] reported on the use of a multisubstrate high-throughput screening for the copper phosphoramidite (**35**) catalyzed enantioselective conjugate addition of diethylzinc to nitroalkenes, using up to nine different aromatic nitroalkenes in a one-pot procedure (Scheme 18) and chiral GC analysis. Very good enantiomeric excesses (among the highest reported for this kind of substrates) were obtained for aromatic (up to 77%) and aliphatic (up to 90%) nitroalkenes.

A library of 125 β-amino sulfonamido-phenolic Schiff bases **36** was prepared in the year 2000 by Gennari, Piarulli, and co-workers in solution using a resin-scavenging protocol to avoid chromatographic purification (Scheme 19).

The library was tested in the enantioselective copper-catalyzed conjugate addition of organozinc reagents to enones[86,87] and nitroalkenes.[88] Good enantiomeric excesses (up to 81% ee) were obtained in the multisubstrate screening (chiral GC) of Et_2Zn addition to cyclohexenone and cycloheptenone (at −20 °C), which were further improved (up to 91% ee) by optimization of the reaction conditions (Scheme 20). Cyclopentenone was not included in the multisubstrate screening, since a clean and enantioselective (up to 80% ee) Et_2Zn addition was obtained running the reaction under different conditions (at 0 °C). It is interesting to note that while the highest enantioselectivities for cyclohexenone and cyclohep-

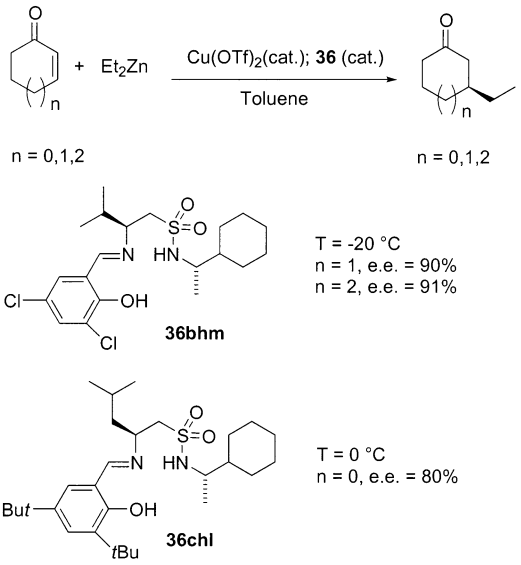
Scheme 19[a]



a; R^1 = Me
b; R^1 = *i*Pr
c; R^1 = *i*Bu
d; R^1 = CH_2Ph
e; R^1 = *t*Bu
f; R^2 = CH_2Ph
g; R^2 = (R) -CH(Me)Cy
h; R^2 = (S) -CH(Me)Cy
i; R^2 = *i*Pr
j; R^2 = $CHPh_2$
k; R^3 = H
l; R^3 = 3,5-*t*Bu_2
m; R^3 = 3,5-Cl_2
n; R^3 = 5,6 -$(CH)_4$-
o; R^3 = 3-Ph

[a] Conditions: [a] methyl trimethylsilyl dimethylketene acetal (MTDA), polymer-bound "dimethylamino pyridine" (20% mol equiv), CH_2Cl_2, 20 °C, 3 h; solid phase bound [tris(2-aminoethyl)amine], 3 h, 86−88%. [b] TFA:CH_2Cl_2 (1:3), 20 °C, 30 min; evaporation; polymer-bound "dimethylamino pyridine", CH_3OH, 20 °C, 24 h, 88%.

Scheme 20

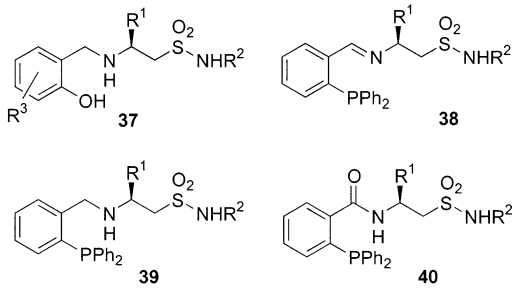


tenone were obtained using the same ligand (**36bhm**), the best results with other enones were obtained using different ligands [cyclopentenone (80% ee), **36chl**; chalcone (50% ee) and benzalacetone (34% ee), **36cho**]. The same library was also screened in the enantioselective copper-catalyzed conjugate addition of diethylzinc to an equimolar mixture of *p*-methylnitrostyrene and *trans*-2-(2-nitrovinyl)thiophene, and the crude reaction mixtures were directly analyzed for conversion and enantiomeric excess determination by chiral GC (57 and 41% ee, respectively, using **36ehm**).

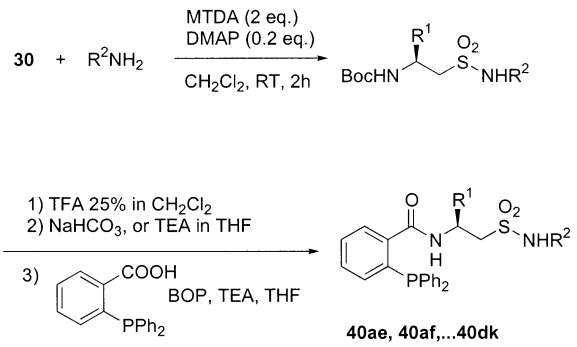
To broaden the scope of this approach, a variation of the ligand structure by transformation or substitution of the phenolic Schiff-base moiety was subsequently undertaken (ligands **37**−**40**, Scheme 21).[89] Preliminary tests in the copper-catalyzed allylic substitution reaction showed some efficacy of ligands **40**.

A small library of ligands **40**, containing the 2-(diphenylphosphino)-benzamide substructure, was prepared varying the residues of the β-amino sul-

Scheme 21

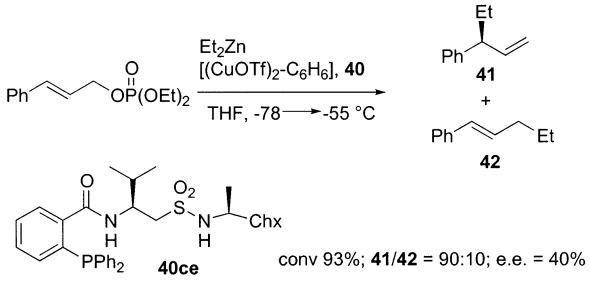


Scheme 22



a; R^1 = CH_2Ph
b; R^1 = Me
c; R^1 = *i*Pr
d; R^1 = *i*Bu
e; R^2 = (S) -CH(Me)Cy
f; R^2 = (R) -CH(Me)Cy
g; R^2 = CH_2Ph
h; R^2 = *i*Pr
i; R^2 = $CHPh_2$
j; R^2 = (S) -CH(*i*Pr)CH_2OH
k; R^2 = (S) -CH(Me)Ph

Scheme 23

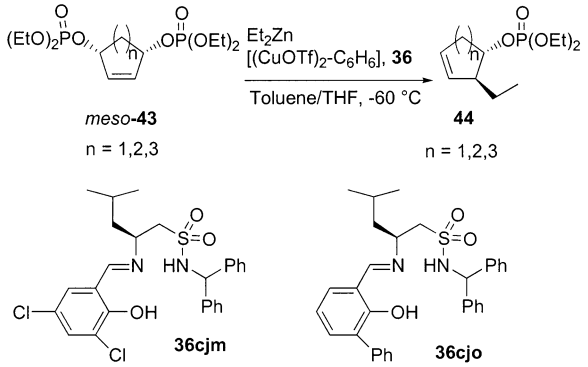


fonamide (R^1) and of the amine moiety (R^2): 14 different ligands were synthesized starting from four β-amino sulfonyl chlorides (R^1 = CH_3, CH_2Ph, *i*Pr, *i*Bu) and seven amines (Scheme 22).[90]

These ligands were screened in the copper-catalyzed [$(CuOTf)_2$-C_6H_6] allylic substitution reaction of cinnamyl phosphate using diethylzinc as a nucleophile (Scheme 23). A good ratio of the S_N2'/S_N2 substitution products (**41**/**42** = 90:10) and a moderate enantioselectivity (**41**,ee = 40%) were obtained using ligand **40ce**.

A new highly regio-, diastereo-, and enantioselective desymmetrization of *meso*, cyclic allylic bisdiethyl phosphates with organozinc reagents catalyzed by copper(I) complexes of chiral Schiff base ligands **36** was recently realized (Scheme 24).[91] The reaction of *meso*-4-cyclopentene-1,3-bisdiethyl phosphate (**43**, n = 1) with diethylzinc was investigated in the presence of 10 mol % $[CuOTf]_2 \cdot C_6H_6$ (Tf = CF_3SO_2) and 10 mol % chiral ligands **36** in toluene:THF (95:5 v/v), at −78 °C. Screening of the library of 125 ligands **36** (see above) afforded the product arising from the S_N2' mechanism with inversion of stereochemistry (**44**, n = 1), with enantiomeric excesses up to 88% (using ligands **36cjm** and **36cjo**). At −60 °C the enantioselectivities remained essentially the same (88% ee) and the yields were improved to ≥98%. A study of the scope of the reaction with different cyclic substrates (six- and seven-membered ring; **43**, n = 2,3) and different organozinc reagents (Me_2Zn and Ph_2Zn) was then undertaken: enantiomeric excesses up to 94% were obtained when Me_2Zn was used in the allylic alkylation of the five-membered ring (**43**, n = 1). Interestingly, moderate ee's (up to 56%) were obtained in a preliminary, incomplete screening with the seven-membered ring (**43**, n = 3), while the six-membered, *meso*-2-cyclohexene-1,4-bis-diethyl phosphate (**43**, n = 2) gave the S_N2' products originating from either inversion or retention of stereochemistry with good diastereoselectivity (81:19−4:96), depending on the solvent and the ligand used. However, in this latter case racemic mixtures were invariably produced.

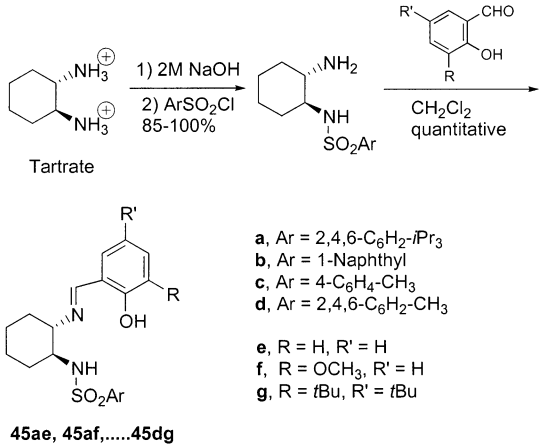
Scheme 24



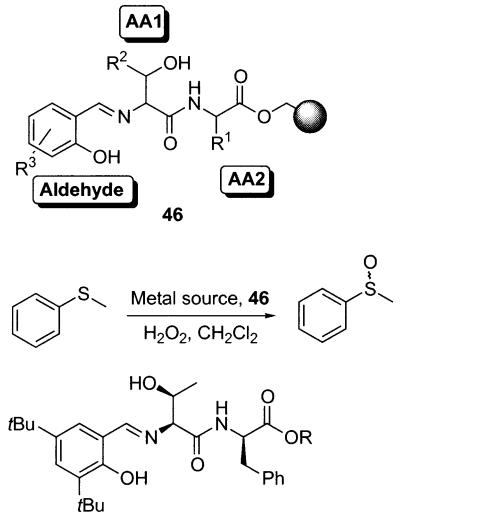
A different approach to modular sulfonamide/Schiff-base ligands (**45**) through a facile two-step synthesis (formation of a monosulfonamide derivative of chiral *trans*-1,2-diamino cyclohexane using several sulfonyl chlorides, followed by condensation with salicylaldehyde derivatives) was reported by Walsh and co-workers (Scheme 25).[92] These ligands were tested in the asymmetric cyclopropanation of allylic alcohols[93] (aryl and alkyl substituted) with the use of zinc−carbenoid reagents. A positional optimization of the sulfonamide and aldehyde substituents was undertaken through an iterative modulation of the aldehyde, sulfonamide, and again aldehyde substituents. Moderate enantioselectivities were obtained (up to 78% ee) using 20 mol % of the ligands, which were improved to 89% ee when 50 mol % ligand was employed.

A library of dipeptide Schiff-base ligands **46** was reported by Jackson and co-workers[94] for the vanadium-catalyzed oxidation of methyl phenyl sulfide using hydrogen peroxide, following the protocol uncovered by Bolm and co-workers (Scheme 26).[95] The ligands were prepared on Wang resin and screened while still attached to the solid support. The vanadyl complexes were preformed by incubation with a solution of $VO(acac)_2$, filtered, and then added to the

Scheme 25

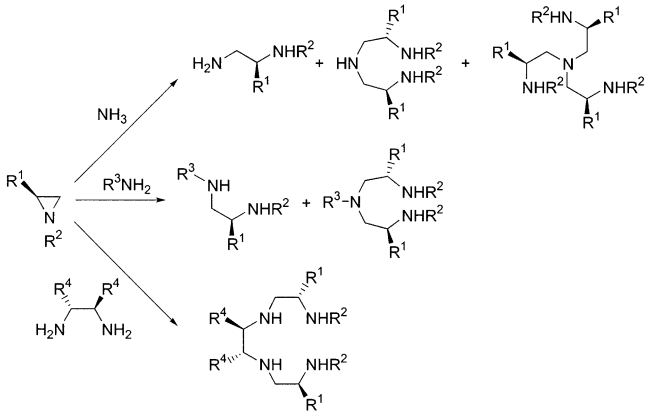


Scheme 26



reaction mixture. After the screening (evaluation of ee's by chiral HPLC) of a first library of 72 members (six AA1, two AA2 and six aldehydes) and identification of *allo*-threonine (Thr*) as the optimal amino acid AA2, a "positional scanning" optimization of AA1 and salicylaldehyde derivatives was performed. The best ligand was then tested with an array of metal sources, from which the optimized Wang-D-Phe-Thr*-DtBS and Ti(O*i*Pr)$_4$ combination emerged (64% enantiomeric excess). Cleavage from the resin by methanolysis (Et_3N/DMF/MeOH) resulted in the ligand methyl ester, which gave an identical 64% ee in the oxidation of methyl phenylsulfide. The scope of this solid-phase-bound catalyst was also investigated in the oxidation of a variety of other alkyl arylsulfides; the ee values were remarkably consistent (ranging from 53% to 72%) with only minor overoxidation of the sulfoxides to sulfones (generally <5%).

Scheme 27

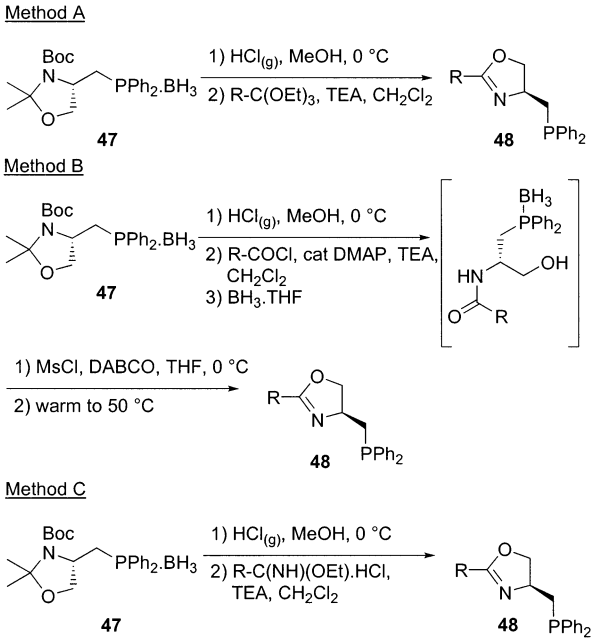


A solid-phase and array approach for the optimization of chiral Schiff-base vanadium catalysts for the enantioselective sulfide oxidation with hydrogen peroxide was reported by Jackson, Anson, and co-workers.[96] A solid-phase-bound salicylaldehyde was first prepared and a library of 29 chiral Schiff bases was synthesized from 29 amino alcohols. The solid-phase screening (similar to the one described above) indicated *tert*-leucinol, amino indanol, and *allo*-threonine methyl ester as the best amino alcohol residues. A second library was then designed, focused on the substituted salicylaldehyde components. 44 diversely substituted salicylaldehydes were condensed in solution with (1*R*,2*S*)-*cis*-amino indanol and tested in the vanadium-catalyzed oxidation of thioanisole with enantiomeric excesses up to 70% and 73% with 3,5-diiodosalicylaldehyde and 1-hydroxy-2-naphthaledyde, respectively. A final optimization using the best amino alcohols (*tert*-leucinol, amino indanol) and salicylaldehydes (3,5-diiodosalicylaldehyde and 1-hydroxy-2-naphthaledyde) increased the enantioselectivity to 90% ee for methyl phenylsulfoxide. Under the optimized conditions, a number of alkyl arylsulfides were oxidized to the corresponding sulfoxides in good isolated yields with enantiomeric excesses in the range 89−97%.

A modular approach to the preparation of chiral, enantiopure sulfonamide ligands with C_1, C_2, and C_3 symmetry was reported in 2002 by Moberg and co-workers via ring opening of chiral *N*-sulfonyl aziridines with ammonia, primary amines, and diamines (Scheme 27).[97] The chiral *N*-sulfonyl aziridines are conveniently accessible from amino alcohols, which, in turn, can be obtained from natural or synthetic amino acids. A library of 23 ligands encompassing 10 different ligand structures derived from two *N*-sulfonyl aziridines (obtained from *S*-alaninol and *S*-valinol) were thus prepared. The new ligands were assessed in the titanium-mediated addition of diethylzinc to benzaldehyde, giving the alcohol product with enantiomeric excess up to 76%.

A parallel approach to the design and optimization of new phosphine oxazoline ligands **48** was reported by Burgess and co-workers (Scheme 28).[98] A divergent approach was devised for the synthesis of the library. This synthetic strategy, as described by Boger and co-workers,[99] "requires that an identical intermediate (preferably an advanced intermediate) be

Scheme 28



converted, separately, to at least two members of the class of compounds." The diphenylphosphine-containing amino alcohol **47**, which is protected at *N*, *O*, and *P*, was chosen as a key advanced intermediate for a divergent synthesis of ligands **48**. After deprotection of the functionalities with a solution of HCl in methanol, formation of the oxazoline was achieved using different methods, depending on the residue (i.e., ortho esters, acyl chlorides, or imidate esters). A small library of 13 ligands was thus prepared and screened for the allylation of malonate with 1,3-diphenylpropenyl acetate.

A special apparatus (Figure 1) was developed for the high-throughput screening of the library of ligands. This consists of a 34-well or a 27-well plate drilled in an aluminum block with a U-shaped internal channel through which cooling fluid can be circulated from a cryostat. A thermocouple was used to check that a uniform temperature was obtained across the plate. The block has the same base size as a 96-well microtiter plate and can be agitated on a microtiter plate shaker; alternatively, stirring bars can be inserted in the wells and magnetic stirring can be used. The reaction mixtures were prepared in glass vials which were then placed in each well. Besides the screen of the ligands, a parallel optimization of the reaction parameters (effect of solvent, chloride ions, and metal-to-ligand ratio) was also performed.

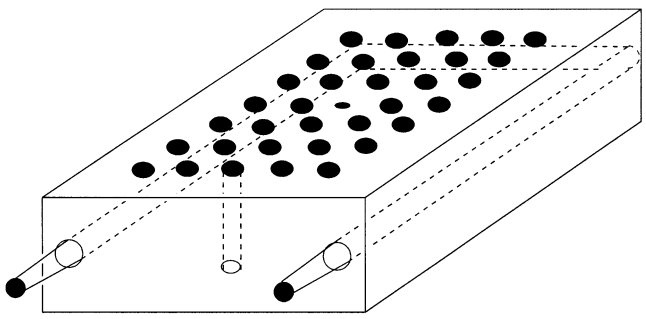
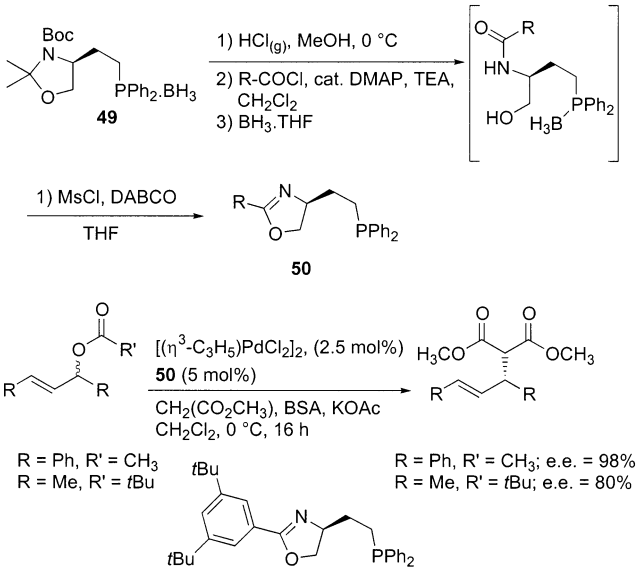


Figure 1.

Scheme 29

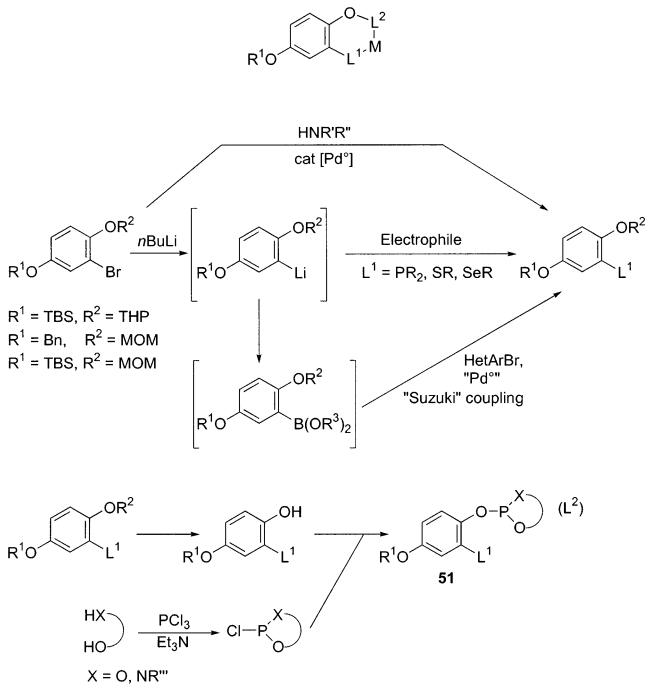


The highest enantiomeric excess (94% ee) was achieved using the adamantyl-substituted ligand in dichloromethane. A sublibrary (seven members) was also screened for the allylation of malonate with 4-pivaloyloxy-2-pentene with enantiomeric excesses as high as 74%.[100] A second generation of modular phosphinoxazoline ligands (JM-PHOS, **50**) with increased chelate ring size was reported by Burgess and co-workers (Scheme 29).[101] The diphenylphosphine-containing amino alcohol **49**, which can be obtained in a few steps from aspartic acid, was chosen as the key advanced intermediate. Deprotection and condensation with carboxylic acid derivatives afforded the JM-PHOS ligands **50**. A few ligands were tested in the allylation of malonate with 1,3-diphenylpropenyl acetate and 4-pivaloyloxy-2-pentene with excellent enantiodiscrimination (98% ee) in the first case and good enantiodiscrimination (up to 80% ee) in the second case.

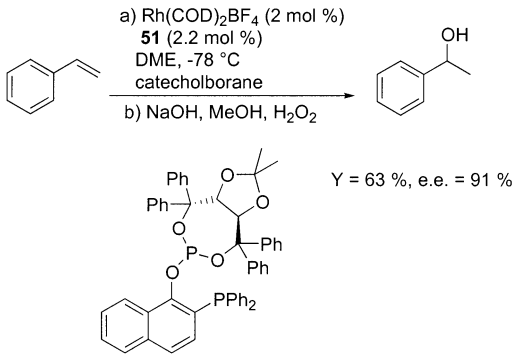
These ligands were also tested in the allylation reaction using 3-acetoxycyclohexene as substrate.[102] Five different ligands were screened, and enantiomeric excesses up to 79% were obtained, with an excellent 95% yield. More recently, a small library (10 members) of JM-PHOS ligands was tested by Burgess and co-workers in the asymmetric hydrogenation of several arylalkenes.[103] High enantioselectivities (up to 95% ee) and conversions (as high as 99%) were observed for some substrates. In those cases where the enantioselectivities were less favorable, it was noticed that a concurrent double-bond migration had occurred.

A modular approach to a new class of structurally diverse bidentate P/N, P/P, P/S, and P/Se chelate ligands (**51**) has been developed by Schmalz and co-workers.[104] Various ligands were synthesized in a divergent manner via orthogonally bis-protected bromohydroquinone as the central building block (Scheme 30). A first donor functionality (L^1) was introduced by lithiation and subsequent treatment with electrophiles (chlorophosphanes, disulfides, diselenides, and carbamoyl chlorides). Alternatively, the lithiated hydroquinone was first transformed into the corre-

Scheme 30



Scheme 31

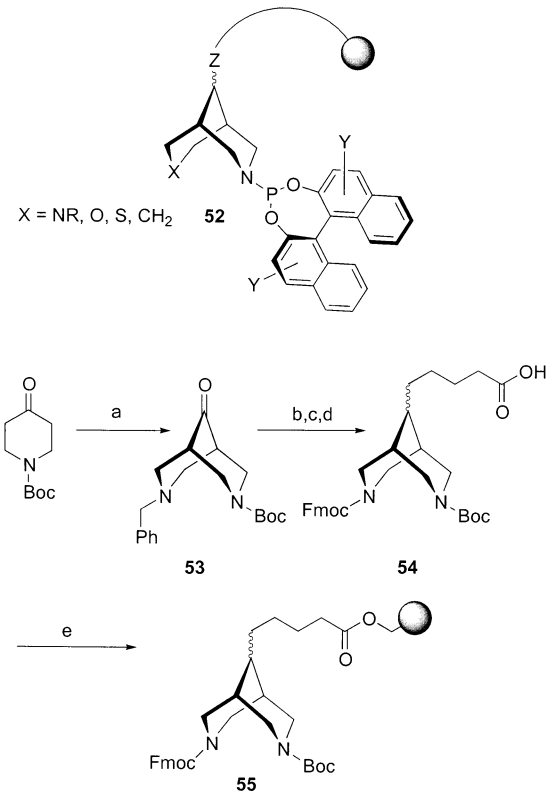


sponding boronic acid and subsequently treated with several heteroarylbromides in the presence of Pd-$(PPh_3)_4$ (Suzuki coupling). As a third general route, the Pd-catalyzed amination was performed on the bromohydroquinone derivative using both primary and secondary alkyl- or arylamines. The derivatives were deprotected (when needed) at the OH *ortho* to the L^1 functionality and coupled to several chlorophosphanes or chlorophosphites to give the L^2 functionality. In addition, 1,5-naphthalenediol and α-naphthol were studied as related backbones.

A library of 20 selected bidentate P/X ligands was tested in the Rh-catalyzed asymmetric hydroboration of styrene (Scheme 31) to give 1-phenylethanol in up to 91% ee (measured by chiral GC or HPLC) after oxidative workup.[105]

A combinatorial approach to a solid-phase library of chiral phosphoramidite ligands (**52**), embodying a binaphthol unit and a bispidine-derived modulating substituent, was recently reported by Waldmann and co-workers (Scheme 32).[106,107] Solution analogues of ligands **52** were successfully employed for the steric steering of Cu-catalyzed enantioselective conjugate addition reactions.[108] The synthesis of a solid-phase-bound library was undertaken in order to find more

Scheme 32[a]



[a] Conditions: (a) $PhCH_2NH_2$, $(HCHO)_n$, AcOH, MeOH, 65 °C, 4 h; (b) $Br^-Ph_3P^+(CH_2)_4COOH$, KOtBu, THF, 0 °C to rt, 2.5 h, 68%; (c) H_2, Pd/C, EtOH, 12 h, rt; (d) FmocCl, $NaHCO_3$, THF, H_2O, 12 h, rt; (e) hydroxymethylpolystyrene, DIC, DMAP, CH_2Cl_2, 12 h, rt. DIC = *N*,*N*′-diisopropylcarbodiimide.

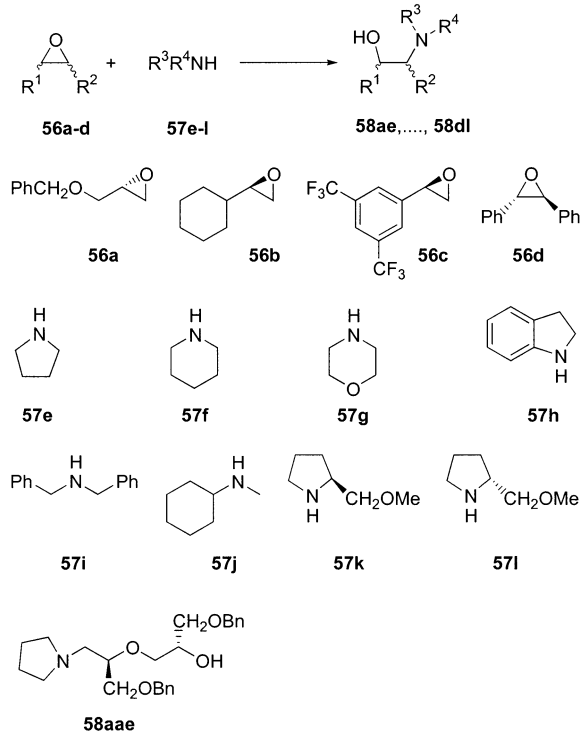
efficient catalysts with the same underlying structural motifs. A modular strategy was envisioned, starting from the orthogonally *N*,*N*-bis-protected bispidinone **53**. Wittig olefination with (4-carboxybutyl)triphenylphosphonium bromide/*t*BuOK, followed by hydrogenolytic removal of the *N*-benzyl group and of the double bond, and Fmoc-protection of the nitrogen afforded scaffold **54**. During the hydrogenation step, the 9-syn and 9-anti diastereomers were formed in a 1:1 ratio which could not be separated either at this or at a later stage. The *N*-Fmoc scaffold (**54**) was coupled to hydroxymethylpolystyrene, and solid-phase-bound scaffold **55** was Fmoc deprotected and derivatized with different (acyl-, sulfonyl-, etc.) groups. In addition, other scaffolds were included featuring a hetero-bispidine nucleus (X = O, S, CH_2) and a substituted piperidine, summing up to five different scaffolds. The various scaffolds were Boc deprotected and transformed into the corresponding phosphoramidites; the phosphoramidite structure of ligands **52** was varied by introduction of different ortho-substituents into the binaphthyl units. Prior to screening in the Cu-catalyzed conjugate addition of Et_2Zn to cyclohexenone, the ligands were converted to the corresponding polymer-bound copper complexes by reaction with copper(II) triflate. A recursive "positional scanning" approach was employed featuring the optimization of the nitrogen substituents in scaffold **52** (X = NR; 57 substituents tested, also including several *N*-acylated and *N*-sulfonylated amino acids and dipeptides).

Optimization of the binaphthyl groups (four substituted binaphthylchlorophosphites were used) was then performed only on the four most promising *N*-substituted bispidine scaffolds; in this screening also the other scaffolds (hetero-bispidines and piperidine) were included. Overall, some 78 solid-supported ligands were tested in the reaction, with an enantiomeric excess up to 67%. To validate the screening of the solid-phase-bound ligands and to prove the concept of ligand optimization on the solid support, five soluble ligands were tested in homogeneous solution and the results were compared with the values determined in the presence of the analogous ligands immobilized on the solid support. In all cases, the results with the soluble ligands were very similar to the supported ones and also the trends gleaned from the solid-phase ligand screening were correctly mirrored.

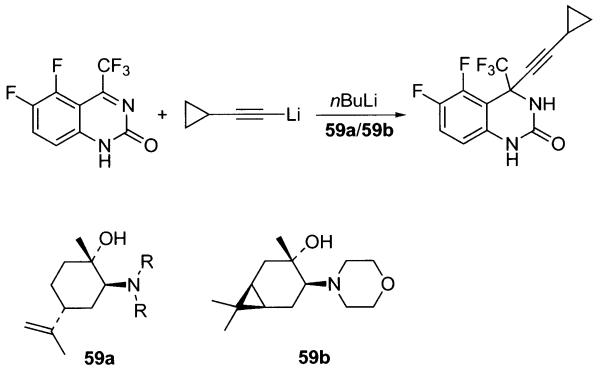
Several approaches to the synthesis of libraries of amino alcohols have appeared in the literature. These are potentially very appealing ligands for a parallel solid-phase optimization due to their easy synthesis starting from amino acids. In 1999 Burguete, Luis, and co-workers reported the synthesis of a small library of polymer-bound chiral β-amino alcohols and used them as chiral auxiliaries for the enantioselective reduction of acetophenone.[109] Three different amino acid methyl esters (derived from Phe, Val, or Leu) were *N*-alkylated with Merrifield resin (PS-1%-DVB-CH_2Cl) and then reduced to the supported primary amino alcohols with $LiAlH_4$ or transformed to the tertiary amino alcohols by reaction with three different aryl Grignard reagents. The reducing agent was prepared using 1 equiv of $LiAlH_4$ and isolated before reaction with the substrate. Conversions were judged by NMR, and enantioselectivities were measured after purification by polarimetry or NMR using chiral lanthanide shift reagents. The screening comprised seven different ligands, and enantiomeric excesses up to 47% were obtained.

In 1998, Nugent and co-workers[110] reported the synthesis of a library of amino alcohol ligands (**58**) which were obtained via the ring opening of epoxides by secondary amines (Scheme 33). The synthesis was performed without the use of any solvent or catalyst upon mixing the two reagents (the epoxide was used in a 5% excess) and heating. A set of four epoxides (**56a**−**d**) and eight commercially available amines (**57e**−**l**) was chosen, and the library of the 32 resulting ligands was screened, without purification, for the addition of diethylzinc to benzaldehyde with ee's as high as 88%. The ligands were also screened after purification by flash chromatography, and overall good correlation with the unpurified ligand results was found. In one particular case (**58ae**) the enantioselectivity was found diminished after purification (74% ee before chromatography and 32% after). Examination of the impurity derived from the synthesis of ligand **58ae** indicated that the crude ligand contained ca. 5% of the 2:1 adduct. This adduct (**58aae**) was independently synthesized and shown to be an efficient catalyst for the addition of Et_2Zn to benzaldehyde, producing 1-phenylethanol in 93% yield and 91% enantiomeric excess.

Scheme 33



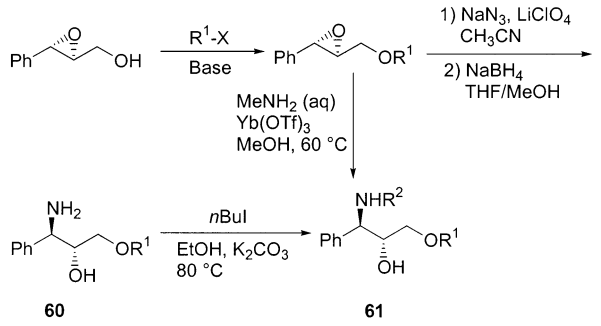
Scheme 34



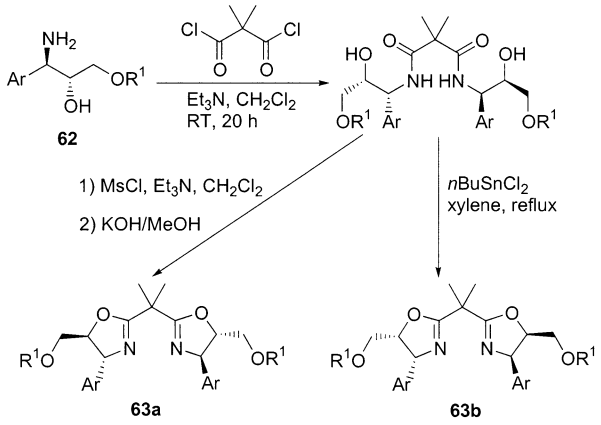
A library of 40 amino alcohols derived from the ring opening of epoxides was also screened by Nugent and co-workers for the addition of lithium cyclopropylacetylide to an unprotected *N*-acylketimine (Scheme 34), which constitutes an efficient route to an important drug candidate used in the treatment of HIV.[111] In general, the addition proceeded with low enantioselectivities (<20%) and limited conversions (<30%). A notable exception was a series of limonene oxide-derived amino alcohols **59a** which promoted the desired addition in up to 74% enantiomeric excess at 84% conversion. To improve this enantioselectivity, the more rigid, "locked" ligand **59b** was developed, starting from carene, which promoted the lithium cyclopropylacetylide addition [in this case lithium bis(trimethylsilyl)amide proved superior to butyllithium or other lithium amides] with a notable 94% enantiomeric excess.

A family of stereodefined, modular amino alcohols (3-alkoxy-1-amino-1-phenyl-2-propanols **60** and **61**) was reported by Pericas and co-workers starting from enantiomerically pure phenylglycidol, prepared by Sharpless epoxidation (Scheme 35).[112] After protec-

Scheme 35



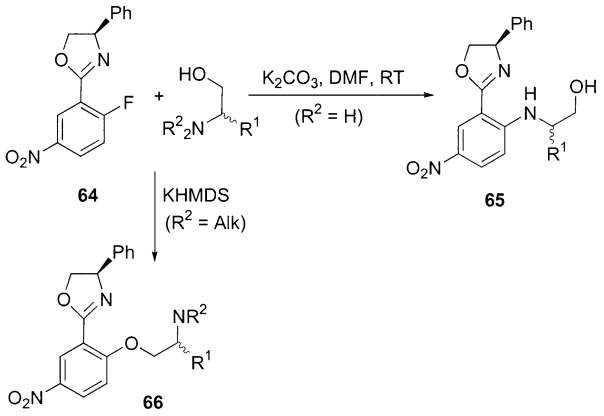
Scheme 36



tion of the primary alcohol with different alkylating agents, the epoxide ring was opened by reaction with sodium azide, reduced to NH_2, and alkylated with *n*-BuI. Alternatively, the epoxide was opened by methylamine the presence of ytterbium triflate (20 mol %). A small library of 10 amino alcohols **60**/**61** was screened in the catalyzed [(amino alcohol)-(arene)Ru(II)] transfer hydrogenation of acetophenone with very good conversions (>90%) and enantiomeric excesses (determined by chiral GC analysis) up to 72%, which were improved to 76% by running the reaction at 0 °C.

In a subsequent work,[113] Pericas, Muller, and co-workers reported the preparation of new families of enantiopure bis(oxazolines) with 4,5-trans (**63a**) or 4,5-cis (**63b**) stereochemistry at the individual rings starting from amino alcohols **62** (Scheme 36), which were prepared as described above for compounds **60**. The 4,5-*trans*-bis(oxazolines) ligands (**63a**) were obtained by reaction with dimethylmalonyldichloride, mesylation of the free OH, and base-induced ring formation, whereas the Desimoni methdology[114] (catalytic nBu_2SnCl_2 and refluxing in xylene) was followed for the 4,5-*cis*-bis(oxazolines) (**63b**), which required retention of configuration at C-2. Ionic palladium complexes containing the nonsubstituted allyl, 1,3-diphenylallyl, and cyclohexenyl groups were prepared from standard palladium materials and the appropriate chiral ligand in the presence of ammonium hexafluorophosphate. These Pd complexes were fully studied by means of NMR spectroscopy. The allyl complexes were then tested in the allylic alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene with dimethyl malonate in dichloromethane at room temperature in the presence of BSA and a catalytic amount

Scheme 37



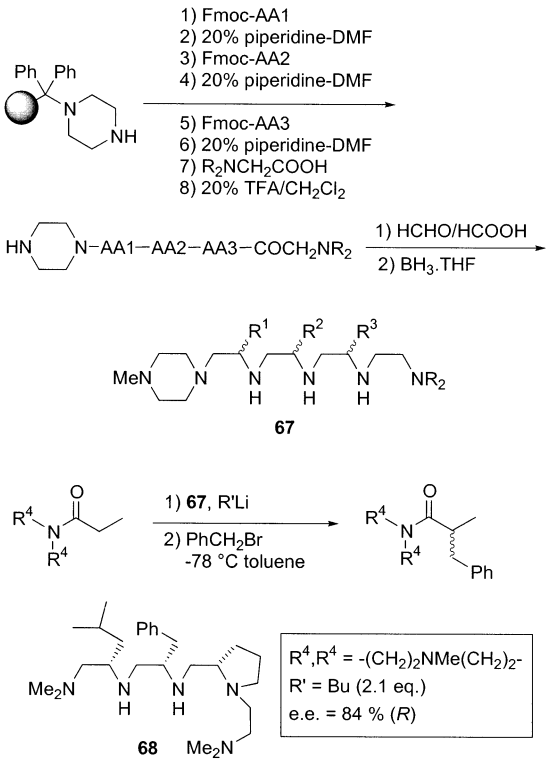
of potassium acetate: 4,5-*trans*-(**63a**)/Pd complexes promoted the enantioselective alkylation with enantiomeric excesses up to 96%, while the 4,5-*cis*-(**63b**)/Pd complex was inactive.

In 1999, Zhu and co-workers reported the synthesis of a new family of *N*,*O* chiral ligands (**65**/**66**) featuring a key aromatic nucleophilic substitution reaction (Scheme 37).[115] In particular, oxazoline **64** was coupled to a number of different amino alcohols yielding exclusively *N*-arylation. The presence of NO_2 group *para* to the fluorine atom was necessary to allow the use of very mild coupling conditions. *O*-Arylation of *N*,*N*-disubstituted amino alcohols was achieved by deprotonation of the hydroxyl using potassium bis-trimethylsilylamide. Application of ligands **65**/**66** in enantioselective catalysis was not reported.

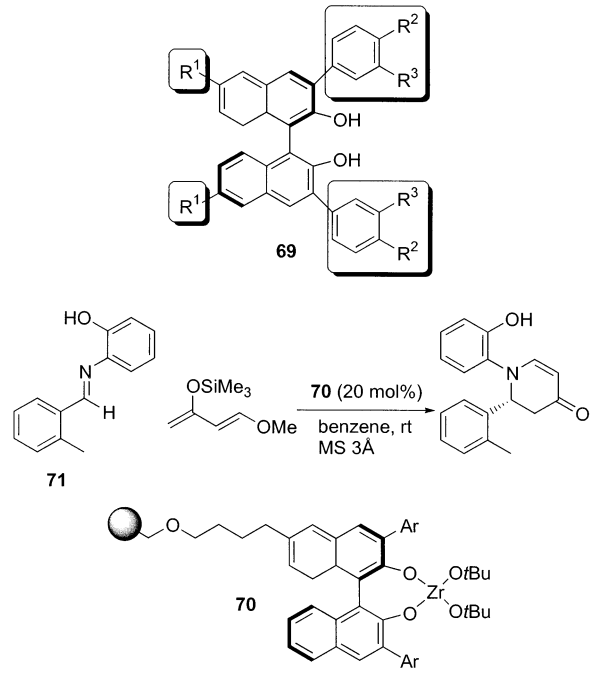
Kobayashi and co-workers reported a novel chiral pentamine ligand (**68**) for the enantioselective α-alkylation of acyclic lithium amide enolates as the result of an optimization of the ligand structure using solid-phase synthesis (Scheme 38).[116] In particular, piperazine was immobilized on trityl-derivatized polystyrene resin, and a tetrapeptide chain with three variable positions and a terminal *N*,*N*-disubstituted glycine residue was grown using standard Fmoc peptide chemistry. Cleavage from the solid support was performed at this stage, and the terminal piperazine secondary amine was reductively methylated (HCHO/ HCOOH). Finally, reduction using BH_3·THF gave the target chiral pentamines (**67**). Optimization of the ligand structure for the benzylation of pyrrolidine propionamide [R,^{4}R^4 = $-(CH_2)_4-$; R′ = Me] was performed using a "positional scanning" approach, and enantiomeric excesses as high as 47% (for the *S* enantiomer) were reported. Further optimization (up to 84% ee for the opposite *R* enantiomer) was obtained changing the terminal *N*-methyl piperazine for dimethylamine and finely tuning the reaction conditions [reaction of *N*-methylpiperazine propionamide, use of BuLi (2.1 equiv) instead of MeLi/LiBr, 1.1 equiv ligand **68**].

A rapid solid-phase/liquid-phase optimization of a chiral Binol ligands **69** for aza Diels−Alder reaction was also reported by Kobayashi and co-workers (Scheme 39).[117] In the preliminary solid-phase approach, 17 polymer-supported 3,3′-aryl disubstituted (*R*)-1,1′-binaphthols were synthesized starting from

Scheme 38

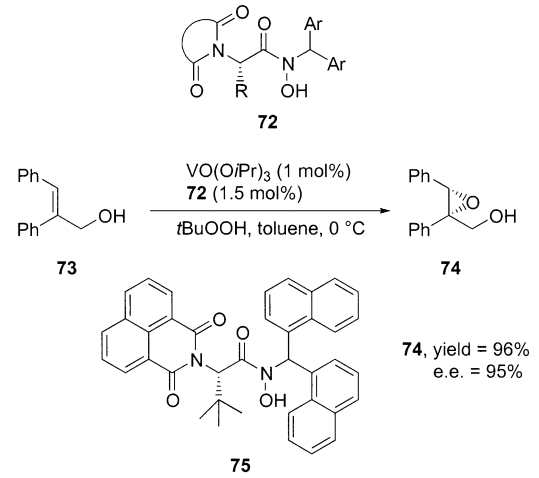


Scheme 39



resin-bound 3,3′-dibromo-(*R*)-1,1′-binaphthol using the Suzuki coupling of different arylboronic acids as the key reaction for the generation of diversity. The solid-supported ligands were transformed into the corresponding zirconium complexes **70** by reaction with Zr(O*t*Bu)$_4$. The model aza Diels−Alder reactions of aldimine **71** with Danishefsky's diene were performed in the presence of 20 mol % zirconium complexes **70** with enantiomeric excesses up to 83%. After the solid-phase optimization of the 3,3′ substituents, a solution optimization of the 6,6′ substituents (H or Br) was undertaken. Also, the source of zirconium was varied [Zr(O*t*Bu)$_4$, Zr(CN)$_4$]. At the end of the optimization procedure, a very good 92% ee was obtained for the model reaction. Investigation of the substrate scope (six imines and two dienes) gave ee's ranging consistently from 83% to 94%.

Scheme 40

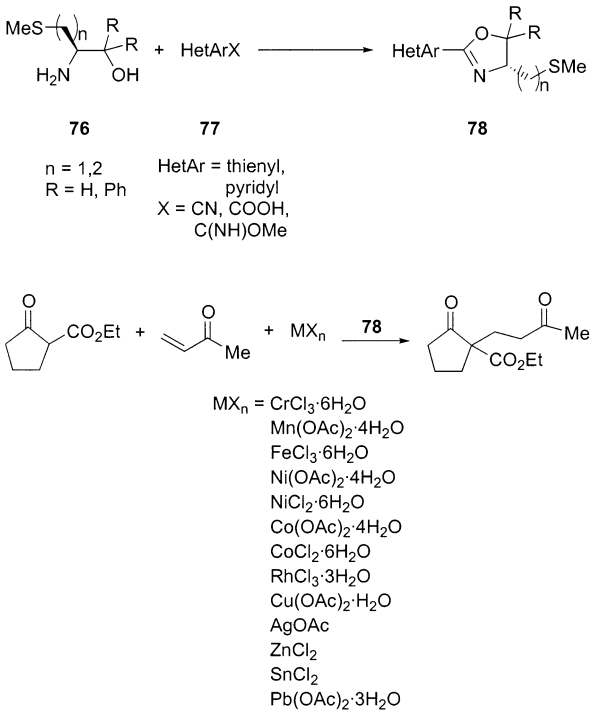


Yamamoto and co-workers described the positional optimization of a family of modular chiral hydroxamic acid ligands (**72**) for the vanadium-catalyzed asymmetric epoxidation of allylic alcohols (Scheme 40).[118] Ligands **72** were obtained from the initial coupling of acid anhydrides (nine anhydrides) with chiral α-amino acids (10 natural amino acids), followed by condensation with diarylmethylhydroxylamines (nine hydroxylamines). Epoxidation of allylic alcohol **73** was performed in the presence of VO(O-*i*-Pr)$_3$ (1 mol %) and ligands **72** (1.5 mol %) at 0 °C for 6 h in toluene with enantiomeric excesses up to 95% (measured by chiral HPLC). Several mono- or disubstituted allylic alcohols were epoxidized with good to excellent selectivity in the presence of optimized ligand **75**. In particular, disubstituted allylic alcohols, except the 3-*cis*-substituted one, were epoxidized with high enantioselectivities (91−95% ee) and yields. Reaction of monosubstituted allylic alcohols, on the other hand, required longer reaction times and gave the corresponding epoxy alcohols with 76−87% ee.

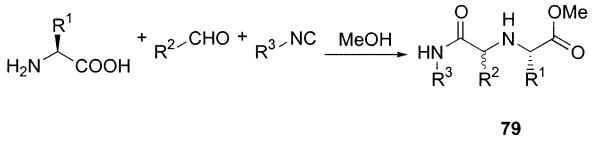
A modular approach to a family of chiral tridentate oxazoline ligands containing thioethers and heteroaryl donor groups was reported by Christoffers and co-workers (Scheme 41).[119] In particular, four amino alcohols **76** derived from the natural α-amino acids L-cysteine and L-methionine were reacted with 2-thiophene and 2-pyridine carboxylic acid derivatives **77** to yield eight tridentate ligands **78** containing an oxazoline, a heteroaryl, and a thioether donor function. These ligands were screened, in combination with 13 different metal salts, for the catalytic asymmetric Michael addition of 2-ethoxycarbonyl cyclopentanone to methyl vinyl ketone with enantiomeric excesses up to 19% (measured by chiral GC).

A modular approach to a new class of chiral ligands (**79**), obtained through a multicomponent reaction, was recently reported by Dyker and co-workers (Scheme 42).[120] In particular, these ligands were obtained by reaction of an amino acid with an aryl aldehyde bearing a Lewis-base functionality and an

Scheme 41



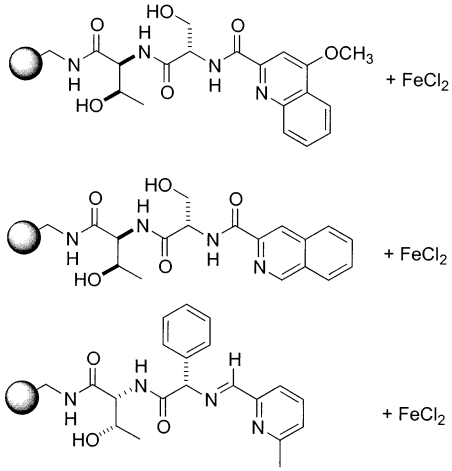
Scheme 42



isocyanide in a nucleophilic solvent (methanol) to yield a 1,1′-iminodicarboxylic acid derivative as a result of the Ugi five-center four-component reaction (U-5C-4CR). A small library (five members) was prepared from the condensation of two aldehydes (2-pyridinecarboxaldehyde and *o*-diphenylphosphinobenzaldehyde) with L-valine and four different isocyanides in anhydrous methanol at room temperature. Two diastereomers were obtained which differed in the configuration at the newly formed stereocenter (the one bearing R^2) with good diastereoselection ($R,S/S,S \approx 9{:}1$). The diastereomeric mixtures were tested as ligands for the Pd-catalyzed allylic substitution reaction of 1,3-diphenylpropenyl acetate with dimethyl malonate with ee values up to 75%. The two diastereomers of the best ligand were separated, and the most abundant diastereomer gave a better 81% enantiomeric excess. Although the size of this library is small, the use of a multicomponent reaction (an approach widely used in pharmaceutical lead discovery) in the generation of a chiral ligand library is new and very promising.

Jacobsen and co-workers discovered novel catalysts for alkene epoxidation using metal-binding combinatorial libraries.[121] First, the entire pooled catalyst library (192 potential ligands and 30 metal ion sources, corresponding to 5760 possible metal−ligand complexes) was screened for compatible epoxidation reaction conditions. This preliminary screening led to the identification of aqueous H_2O_2 as a viable oxidant. In the second screening stage, catalyst

Chart 2

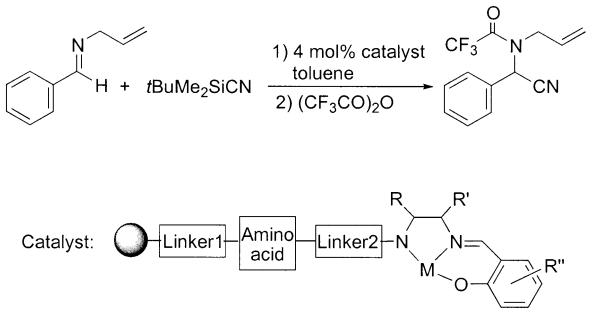


sublibraries were prepared that contained a mixture of all 192 ligands and each individual metal source (30). Upon determining, with this screening, that $FeCl_2$-derived libraries displayed ligand-promoted epoxidation catalysis, the third step in the screening process was to identify the ligand components necessary for catalytic activity. The 192 ligand structures were evaluated individually: following metal complex formation with $FeCl_2$, each library member was screened in a parallel fashion for epoxidation of *trans*-*β*-methylstyrene with 30% H_2O_2. In this way, the ligand structures that produced catalysts that were substantially more active than other structures in the library were identified. Finally, a parallel library of 96 ligands was prepared and screened for enantioselective catalysis, which led to the identification of the structures shown in Chart 2 as moderately enantioselective catalysts (ee ≤ 20%). Up to 78% conversion of *trans*-*β*-methylstyrene was obtained (with the epoxide as the sole reaction product) by using the optimized reaction conditions of 1.5 equiv of 30% H_2O_2 and 5 mol % of chiral ligand.

III. Libraries of Chiral Organic Catalysts with a Modular Structure (Synthesis and Screening)

Many enzymes are remarkable asymmetric catalysts, and most of them do not make any use of metal ions to perform their catalytic activity: the presence of suitably arranged purely organic reactive sites is sufficient to drive forward the reaction in high yield and, often, extremely high enantioselectivity. More recently, synthetic chemists have started using small organic molecules as catalysts to realize highly enantioselective transformations.[122,123] In fact, organic catalysts show several synthetic advantages: (i) usually the reactions can be performed under an aerobic atmosphere, with wet solvents; (ii) the catalysts are inexpensive; (iii) they are often more stable than enzymes or other bioorganic catalysts; (iv) the small organic molecules can be attached to a solid support and recycled more easily than the metal-based catalysts; and (v) finally, they are highly modular, allowing for easy optimization using combinatorial and high-throughput strategies. It is therefore not surprising that the generation and screening of combinatorial parallel libraries has become an

Scheme 43



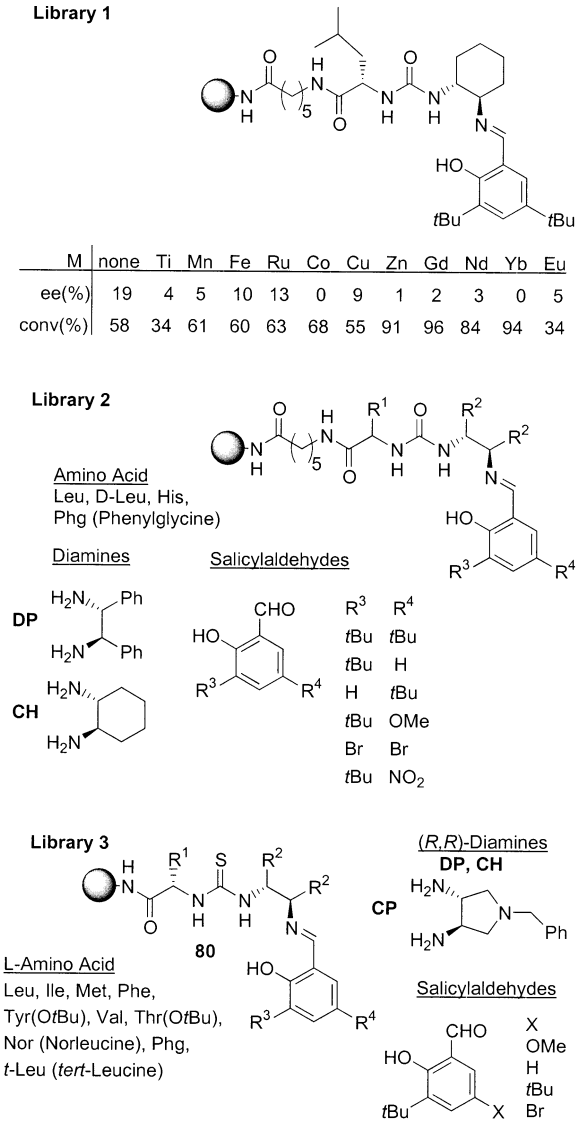
extremely useful tool for the optimization of the structure of organic catalysts.

The first example was reported by Jacobsen and co-workers with the solid-phase synthesis of a parallel library of tridentate Schiff bases and its screening in the asymmetric hydrocyanation of imines (the Strecker reaction) by addition of TBSCN to *N*-allylbenzaldimine (Scheme 43).[124] The ligand structure comprised a salicylaldehyde derivative, a chiral diamine, with the second nitrogen of the chiral backbone serving as the site of attachment to the solid support (Scheme 43). An amino acid was incorporated as an additional diversity element between the diamine and the solid support.

An iterative optimization of reaction enantioselectivity was then performed in three phases (Scheme 44): (i) one ligand was prepared and evaluated for the catalytic reaction in the presence of a series of 11 different metal ions. It was thus discovered that the best ee was obtained in the absence of any added metal ion. (ii) On the basis of this initial result, a parallel library of 48 catalysts was prepared on the solid phase and screened to investigate the role of the various components of the ligand structure. It was observed that the following were important features: the amino acid substituent, the relative stereochemistry of the diamine versus the amino acid, and the aldehyde substituents. In addition, control experiments highlighted that "linker 1" (γ-amino caproic acid) had a deleterious effect promoting a significant background reaction and that also "linker 2" played a role in the tuning of the enantioselectivity, with the thiourea derivative being superior to both urea- and guanidine-based systems. (iii) From this information, a more focused library of 132 thiourea derivatives was prepared incorporating only nonpolar L-amino acids and 3-*tert*-butyl-substituted salicylaldehydes. Screening of the supported library for the Strecker reaction and evaluation of the enantioselectivities by chiral HPLC identified **80** ($R^1 = t$-Bu; $R^2,R^2 = -(CH_2)_4-$; $R^3 = t$-Bu; $R^4 =$ OMe) as the best catalyst, affording the highest enantiomeric excess (80%).

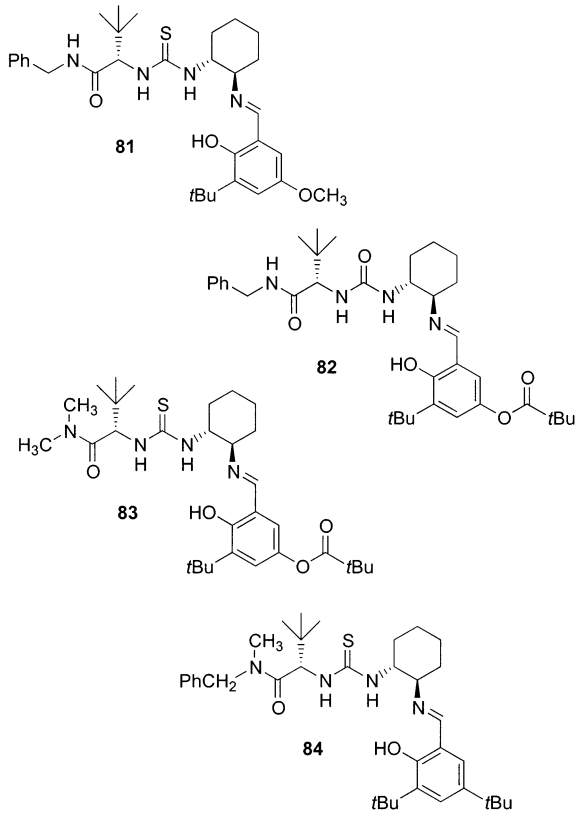
The best catalyst was resynthesized in solution [with benzylamine at the C-terminus (**81**), Scheme 45] and tested in the asymmetric Strecker reaction using HCN as cyanide source and different allyl aldimines (aromatic and aliphatic), with enantiomeric excesses ranging from 83% to 91%. An improvement to this methodology was later reported by the same group,[125] screening a new solid-phase-bound, second-generation library of 70 catalysts,

Scheme 44

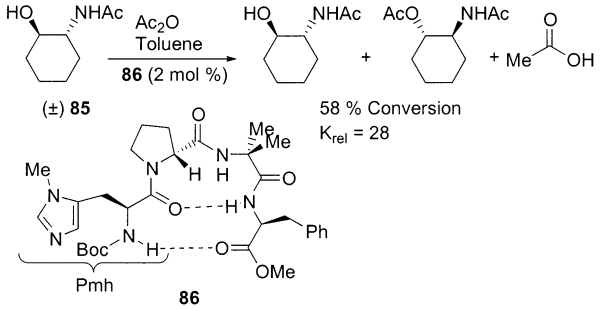


incorporating seven amino acids with large α-substituents and 10 salicylaldehyde derivatives. From the screening, catalyst **80** [$R^1 = t$-Bu; $R^2,R^2 = -(CH_2)_4-$; $R^3 = t$-Bu; $R^4 =$ OCO(*t*Bu)] and its solution analogue **82** (Scheme 45) featuring benzylamine at the C-terminus and urea as "linker 2" were identified as the best catalysts for the formation of the Strecker adduct (75% yield and 95% ee). The scope of the asymmetric Strecker reaction proved to be broad with aryl as well as benzylic and aliphatic imines, giving ee's ranging from 80% to 95%. In general, the resin-bound catalyst **80** was only slightly less selective (2−4%) than its solution analogue, but it holds the practical advantage that it can be easily removed by filtration and reused as it is. In fact, no loss of catalyst activity or product enantioselectivity were observed even after 10 catalyst recycles. Highly enantioselective addition of HCN to *N*-protected ketoimines was also reported[126] using the same ligand **82**. Essentially quantitative isolated yields and enantiomeric excesses higher than 85% were obtained for *N*-benzyl aryl methyl imines. A practical solution-phase synthesis of **82** was reported which gives the ligand in 80% overall yield after four steps without the need for any chromatographic purifica-

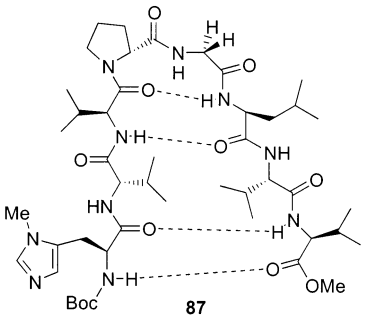
Scheme 45



Scheme 46



Scheme 47



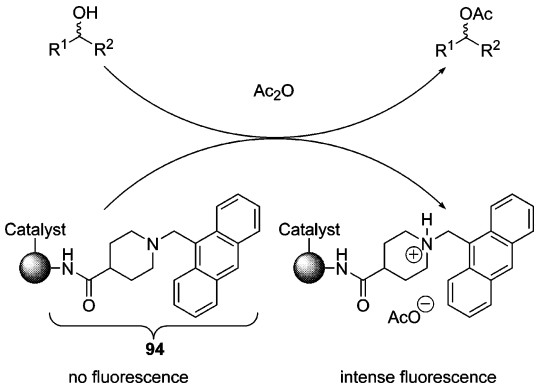
87: Boc-Pmh-Val-Val-D-Pro-Gly-Leu-Val-Val-OMe
88: Boc-Val-Pmh-Val-D-Pro-Gly-Leu-Val-Val-OMe
89: Boc-Val-Val-Pmh-D-Pro-Gly-Leu-Val-Val-OMe
90: Boc-Val-Val-Val-D-Pro-Gly-Pmh-Val-Val-OMe
91: Boc-Val-Val-Val-D-Pro-Gly-Leu-Pmh-Val-OMe

tion.[127] The origin of the excellent selectivity of this ligand and the mechanism of the Strecker reaction were studied in detail,[128] and it was discovered that (i) the catalyst adopts a well-defined secondary structure in solution, (ii) the mechanism involves a reversible formation of an imine−catalyst complex through a hydrogen bond between the imine nitrogen and the urea hydrogens, (iii) the imine reacts as its *Z* stereoisomer, (iv) the imine binds to the chiral pocket with the large substituent pointing outward in the solvent and the smaller substituent (H or Me) toward the interior of the catalyst, (v) the imine *N*-substituent is also pointing toward the solvent and therefore its steric hindrance is not crucial, apart from destabilizing the *Z* isomer if it becomes too bulky. On the basis of this mechanistic scenario, **83** (Scheme 45) featuring dimethylamine at the C-terminus and thiourea as "linker 2" was prepared and proved to be the best catalyst for the Strecker reaction (ee 97%). In addition, these ligands are also effective for the activation of imines toward other interesting carbon-based nucleophiles, in particular enolate equivalents. In fact, reaction of benzaldehyde *N*-Boc imine with the trimethylsilyl ketene acetal of methyl acetate (3 equiv) in the presence of **82** (10 mol %) afforded the desired Mannich adduct with good conversion and enantiomeric excess of 47%.[129] Catalyst optimization was achieved through the construction of a small, parallel library of 22 compounds, with systematic variation of salicylaldehyde, diamine, amino acid, and amide components. Catalyst **84** (*N*-benzyl,*N*-methylamine at the C-terminus, thiourea as "linker 2") obtained from the screening of this small library proved remarkably selective and broad in scope: yields higher that 84% and high enantioselectivities (≥87% ee) were obtained with a number of *ortho*-, *meta*-, and *para*-substituted arylaldimines.

Miller and co-workers have showed that short peptides containing *N*-alkylated histidine residues can be used as catalyst for the enantioselective acylation of secondary and some tertiary alcohols. The *N*-alkylated histidine residues are postulated to facilitate acylation by a nucleophilic mechanism, whereas the backbone amides and side chain functionalities are supposed to govern the selectivity through enantiomer-specific secondary contacts (hydrogen bonding, π-stacking, ion pairing, etc.). In preliminary studies on the kinetic resolution of racemic *trans*-2-acetamido-1-cyclohexanol (**85**) with acetic anhydride, very good results in terms of k_{rel} (k_{fast}/k_{slow}) were obtained with the minimal β-hairpin peptide **86**, containing the β-turn-inducing motif D-Pro-Aib and the π-(Me)-histidine (Pmh) residue (Scheme 46).[123,130]

A small parallel solid-phase library of five conformationally biased octapeptides (**87**−**91**), containing the common D-Pro-Gly motif at the turn region (*i*+3 to *i*+4) and the Pmh residue, was prepared by standard solid-phase peptide synthesis on PS−HMBA resin (Scheme 47).[131] The Pmh residue was coupled at the *i*, *i*+1, *i*+2, *i*+5, and *i*+6 positions while maintaining all the other positions constant. The catalytic peptides were screened for their ability to promote the kinetic resolution of five- (**92**), six- (**85**) and seven-membered (**93**) *trans*-2-acetamido-1-cycloalkanols. Very good results (K_{rel} = 51 for **85**, 27 for **92**, 15 for **93**; conversions 45−50%) were found using catalytic peptide **87**, which shows the Pmh residue in the *i* position; interestingly, peptide **88**, which contains the Pmh residue in the *i*+1 position,

Scheme 48

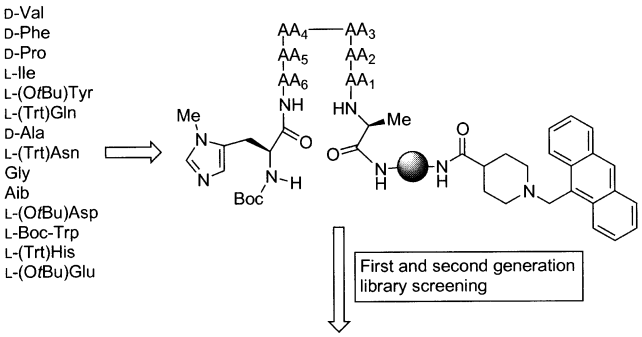


is moderately selective (K_{rel} = 8 for **85**, 9 for **92**, 12 for **93**; conversions 49−55%) in favor of the other enantiomer.

Unfortunately, this type of catalysts gave disappointing results when a hydrogen-bonding handle (such as the acetamido group) is lacking in the substrate (K_{rel} < 2 for 1-phenylethanol).[132] To address this problem, Miller and co-workers reported the synthesis of a split and pool library for the kinetic resolution of secondary alcohols (without a hydrogen-bonding handle).[132] A specifically developed fluorescence-based assay[133] was employed for the screening of the library. This assay is based on the observation that, in these kinetic resolutions, the most enantioselective catalyst typically afforded the fastest reaction. Since these transformations produce an equivalent of acetic acid for each catalytic turnover, a pH-sensitive fluorescence sensor would detect acetic acid evolution and therefore catalyst activity. The chosen fluorescence sensor was the aminomethylanthracene derivative **94** which was coupled via a phenylalanine linker to Wang resin (Scheme 48). Control experiments, where known acylation catalysts were loaded onto the same beads as the sensor, revealed that the beads carrying the most effective catalysts became highly fluorescent if placed in a medium where both acetic anhydride and *trans*-2-acetamido-1-cycloalkanol were present. It must be emphasized that the fluorescent signal is coupled to catalyst activity but not to the degree of enantioselectivity that a particular catalyst may afford. The assay can be fruitfully employed only under the hypothesis that the most active catalyst is also the most enantioselective one.

A highly diverse library of octapeptides was synthesized on resin beads, such that each individual bead was co-functionalized with (i) a uniform loading of the pH-sensitive fluorophore **94** and (ii) a unique peptide-based catalyst. The octapeptide format was selected wherein the first and last amino acids were held constant with alanine and π-(Me)-histidine (Pmh), respectively (Scheme 49). Fourteen unique amino acid monomers were then incorporated in the remaining six positions using the split and pool method. The theoretical diversity of this library (14^6) is 7.5 million unique catalysts. The number of beads was used for limiting the size of the library: since approximately 100000−125000 beads were used for the synthesis, the library at maximum contained the same number (ca. 100000) of unique peptide catalysts

Scheme 49. Structure of the Library of Randomly Chosen Octapeptides and of the Peptide-Based Catalyst 95

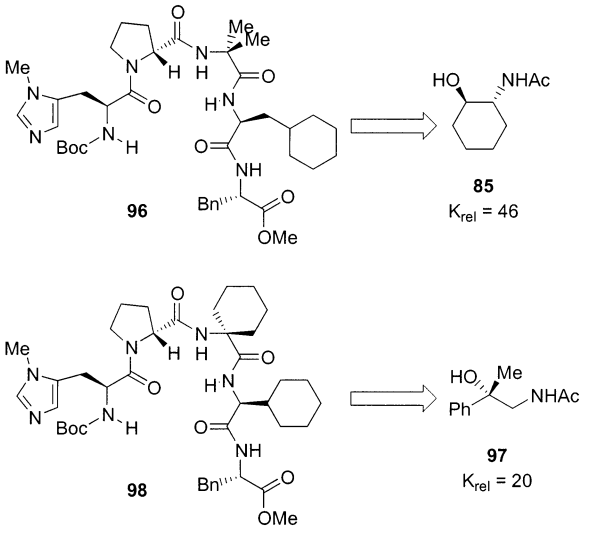


95: Boc-Pmh-(*t*Bu)Thr-D-Val-(Trt)His-D-Phe-D-Val-(*t*Bu)Thr-Ile-NH*n*Pr

on beads uniformly loaded with the fluorophore. A sample of the library was selected at random and screened for activity in the acylation of racemic 1-phenylethanol with acetic anhydride in toluene at room temperature. Among the most active catalysts, a lead peptide was identified (Edman degradation) that provided a K_{rel} = 8.2 upon resynthesis and evaluation under homogeneous conditions. A second-generation split and pool library was synthesized such that the members were biased toward the lead structure. In practice, the beads were partitioned unevenly at each split step: 65% of the beads were functionalized with the residue corresponding to that of parent lead peptide at each position. The remaining 35% of the beads were divided into 14 equal portions and coupled to 14 different amino acids. Also, in this case the library size was limited by the number of beads used in the split and pool synthesis and approximately 6000 unique structure were represented. The library was independently synthesized twice: once on Wang resin and the second time on beads that were co-functionalized with both a permanent noncleavable linker and a safety catch linker. In the first case (Wang resin) the screening was conducted on beads, whereas in the second case (safety catch linker) the catalysts were directly cleaved into a multiwell plate. Random samples of the second-generation library were screened in single-bead assays, and several new peptide-based catalysts were identified that afforded improved selectivities. In particular, peptide **95** proved effective for the kinetic resolution of 1-phenylethanol (k_{rel} = 20, measured by chiral GC) as well as other secondary alcohols (k_{rel} = 4−50). It is very interesting to note that the peptides identified from this combinatorial approach do not contain sequences inducing a secondary structure and hence would not be predictable based on a solely rational approach.

A fluorescence-based screening of asymmetric acylation catalysts through parallel enantiomer analysis was later reported by Miller and co-workers.[134] To obtain information concerning relative rates of reaction for two different enantiomers of a secondary or tertiary alcohol, each catalyst was screened for reactivity against the isolated, optically pure enantiomers of the starting materials. In practice, a multiwell plate was divided in half, with one enantiomer deposited in one-half of the wells (e.g., 48 wells

Scheme 50

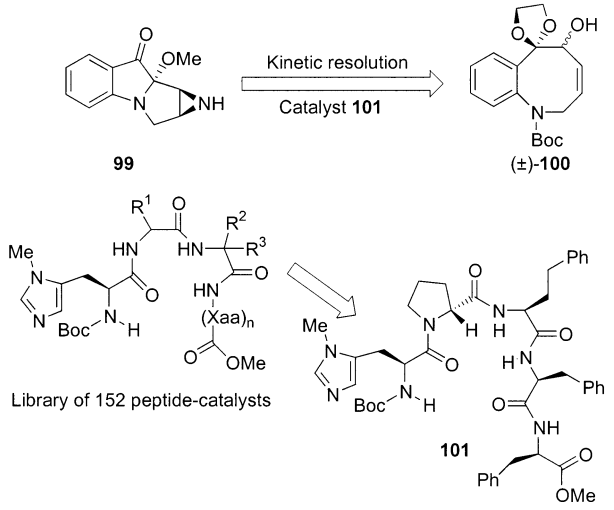


in a 96-well plate) and the other enantiomer in the remaining wells. A fluorescence plate reader allowed for simultaneous determination of the relative rates of 48 catalysts toward the two enantiomers. A first library of 60 tetra- and pentapeptides containing a β-turn-inducing sequence and the catalytically active Pmh monomer was synthesized in parallel on solid phase; the peptides were cleaved from the resin by methanolysis and directly used in the screening assay. One peptide (**96**) was identified which catalyzed the kinetic resolution of *trans*-2-acetamidocyclohexanol (**85**) with $k_{rel} = 46$ (Scheme 50). The same library was also screened for the acylation of tertiary acetamido alcohol **97**, and peptide **98** was identified as the best catalyst ($k_{rel} = 20$ at 4 °C; 47% conversion). The β-turn bias seems to be essential for the kinetic resolution of these substrates; in fact, the screening of a library of pentapeptides (75 members, randomly chosen from a theoretical library size of 8192) that contained no β-turn-inducing sequence exhibited $k_{rel} < 2.0$.

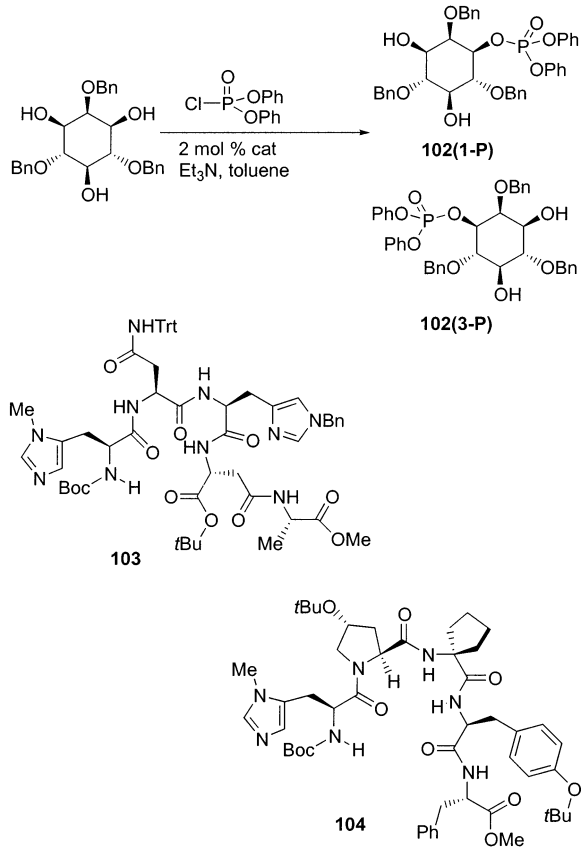
The application of a combinatorial peptide library for kinetic resolution of racemic alcohols to the synthesis of natural products was also reported.[135] In particular, the asymmetric synthesis of the tetracyclic mitosane **99** was achieved through the enantioselective acylation of the racemic secondary alcohol **100** (Scheme 51). The identification of a catalyst for the kinetic resolution of **100** required the screening of a diverse set of catalyst candidates; for this, 152 peptides with the general structure reported in Scheme 51 were prepared by solid-phase synthesis and cleavage in solution (methanolysis). Screening of the unpurified catalysts at room temperature for kinetic resolution of compound **100** resulted in selectivity factors (k_{rel}) that ranged from 1 to 10. Peptide **101**, in particular, proved to be promising and was therefore purified to homogeneity for further study. Optimization of the reaction conditions (addition of 6 equiv of Et_3N at 0 °C) improved the observed k_{rel} value to 27.

Miller and co-workers reported also a very nice example on the screening of combinatorial libraries of peptide catalysts for the enantiodivergent phos-

Scheme 51

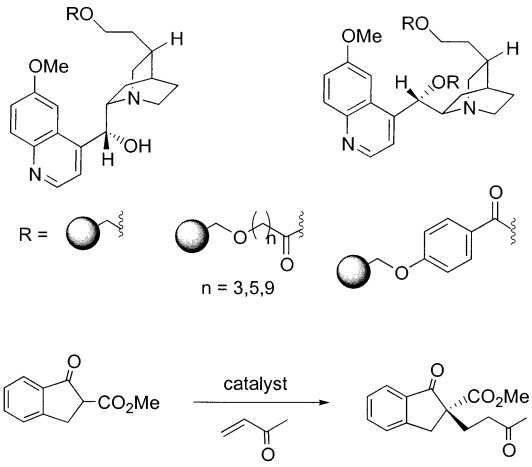


Scheme 52



phorylation of a *meso myo*-inositol derivative (2,4,6-tri-*O*-benzyl-*myo*-inositol) (Scheme 52).[136,137] In fact, whereas many synthetic catalysts may be obtained in both enantiomeric forms to produce either enantiomer of the products of a catalyzed reaction, in the case of peptide-based catalysts, this is not practical due to the limited availability and high cost of the D-amino acids. In nature, enzymes, due to their ability to adopt highly diverse tridimensional structures, can achieve opposite enantioselectivities, thus providing complementary enantiospecificities. To achieve the same goal with small peptide libraries, the screening of a combination of random and focused peptide libraries containing the basic residue π-(Me)-histidine (Pmh) (178 tetra- through octapeptides) was

Scheme 53

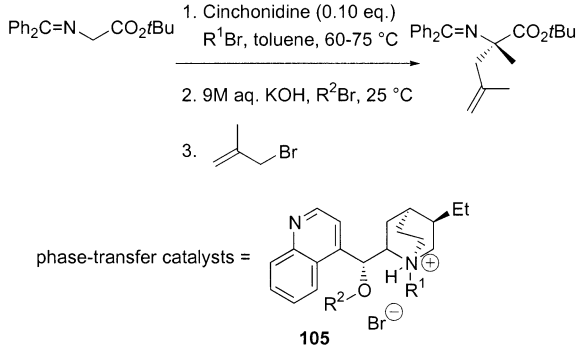


undertaken. An initial 39-membered-library, based on randomly chosen peptides, also including some sequences that were biased to form ***β***-turns and ***β***-hairpins in organic solvents, was prepared on the solid phase (Wang polystyrene resin), and catalysts were cleaved (methanolysis) before screening. A two-stage achiral/chiral HPLC assay was adopted for the determination of the overall product distribution (achiral preparative HPLC) and enantioselectivity of the phosphorylation (chiral analytical HPLC). Very good enantiomeric excess in favor of the formation of **102(1-P)** (90% ee) was obtained with peptide **103**, which did not possess any conformational bias, while only modest enantioselectivities were observed for the formation of the enantiomer **102(3-P)**. For this reason an expanded library of 97 pentapeptides was designed, also using a randomization algorithm to achieve highly diverse sequences. From this additional screening, two peptides containing the *β*-turn-inducing sequence were identified as moderately selective (57 and 65% ee) for the formation of **102-(3-P)**. A new 42-membered focused library was designed around these leads. From the screening of this library some common features emerged which once combined in peptide **104** afforded **102(3-P)** in 94% ee at 70% conversion.

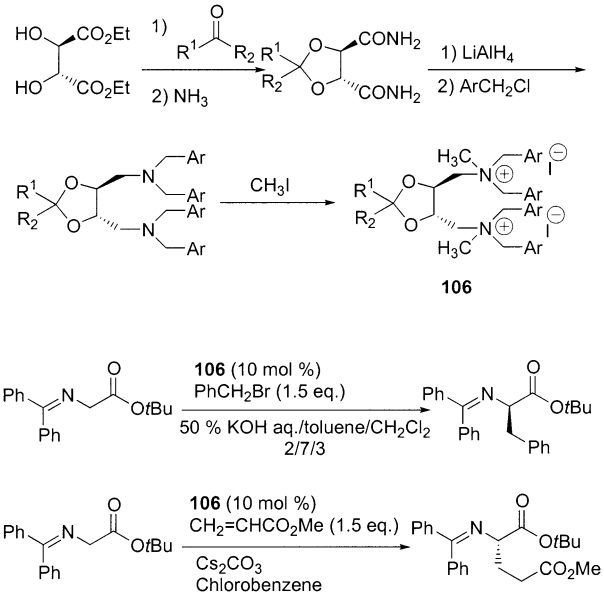
A small library (10 members) of polymer-supported *Cinchona* alkaloids derivatives was reported by Cavé, D'Angelo, and co-workers (Scheme 53).[138] Two pseudoenantiomeric quinine and quinidine derivatives were coupled to Merrifield resin by means of different spacers (three alkyl spacers of different length, *p*-hydroxybenzoic acid and no spacer at all). The polymer-supported amino alcohols were then screened for the asymmetric Michael addition of methyl vinyl ketone to 2-carbomethoxy-1-indanone with ee's up to 87%.

A small library of quaternary dihydrocinchonidine-derived ammonium salts (**105**) was screened by Lygo and co-workers as phase-transfer catalysts for the asymmetric alkylation of glycine imines (Scheme 54).[139] In particular, 20 different *N*,*O*-bisalkyldihydrocinchonidinium salts were prepared in situ by quaternarization of the basic dihydrocinchonidine nitrogen with five alkyl bromides (R^1Br) in hot toluene, followed by etherification of the hydroxy group with the same or different alkyl bromides (R^2-

Scheme 54



Scheme 55

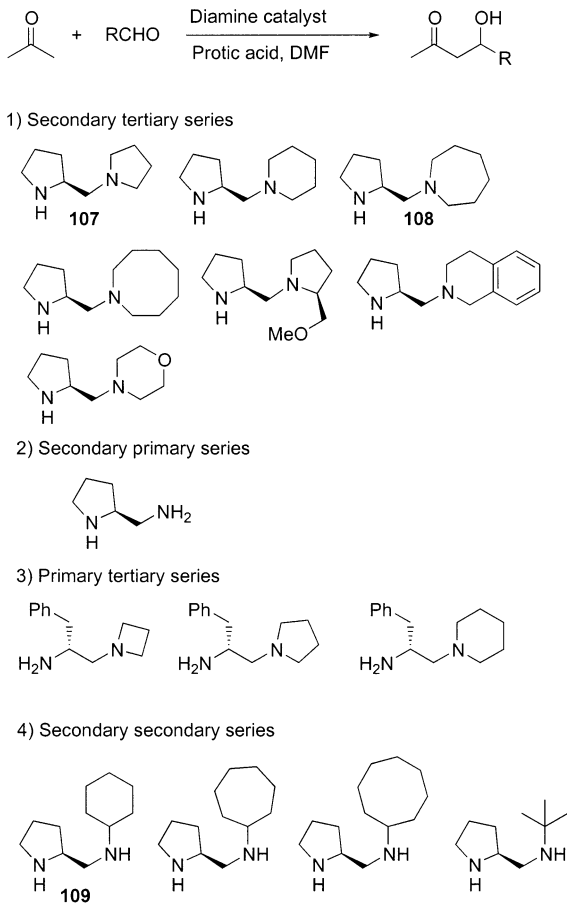


Br) upon addition of 9 M aqueous KOH and stirring at RT. Benzophenone-derived glycine imine was then added together with a third alkylating agent (e.g., methallyl bromide) and the reaction stirred until completion. Enantioselectivities were measured by chiral HPLC, and ee's up to 93% were obtained.

A library of asymmetric two-center catalysts for phase-transfer reactions was reported by Shibasaki and co-workers.[140] The catalysts (**106**) were easily synthesized starting from L- or D-tartrate using a variety of ketal moieties (R^1 and R^2) and aromatic parts (Ar) (Scheme 55). The catalysts (>40) were screened for the phase-transfer alkylation of benzophenone-derived glycine imine with benzyl bromide (ee's up to 70%) and the Michael addition of benzophenone-derived glycine imine to methyl acrylate (ee's up to 64%). Tuning of the reaction parameters (base, solvent, and temperature) using the two different optimized ligands increased the enantiomeric excesses to 93% and 75% for the alkylation and Michael addition reaction, respectively.

Yamamoto and co-workers described a diversity-based strategy for the asymmetric catalysis of direct aldol reaction using a diamine/protic acid system.[141,142] In a preliminary experiment, reaction of *p*-NO_2benzaldehyde with acetone in DMF in the presence of 3% *p*-toluenesulfonic acid and diamine **107** yielded the aldol condensation product in 19%

Scheme 56

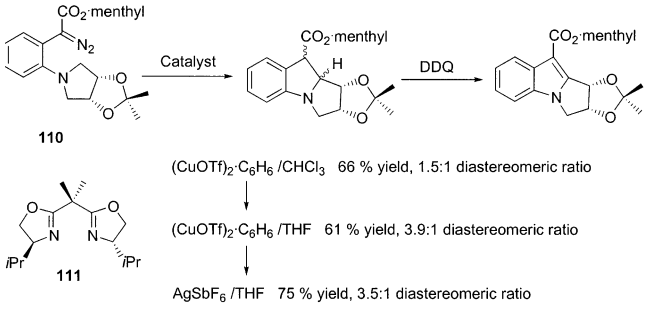


yield and 83% enantiomeric excess, along with 3% of the dehydration product (Scheme 56). An optimization of the reaction conditions was then undertaken screening different protic acids (five including Tf_3-CH, *o,p*-dinitrobenzenesulfonic, *p*-toluenesulfonic, benzoic, and triflic acid) and different solvent systems (THF, DMSO, MeOH, CH_3CN, and acetone, which gave the best results). A small collection of diamines (Scheme 56) derived from L-proline (with a secondary−primary, secondary−secondary, and secondary−tertiary structure) and from D-phenylalanine (with a primary−tertiary structure) were synthesized and screened for three different aldehydes (*p*-NO_2-benzaldehyde, benzaldehyde, and cyclohexane carboxaldehyde) using *o,p*-dinitrobenzenesulfonic acid. The enantiomeric excesses were measured by chiral HPLC; the L-Pro- and D-Phe-derived catalysts gave opposite enantioselectivities. The best results were obtained using diamine **108** (limited to *p*-NO_2-benzaldehyde, ee = 93%) and diamine **109** [slightly lower ee's with *p*-NO_2benzaldehyde (ee = 81%) but reasonable yields and good ee's also with the other two aldehydes (ee's = 74−80%)].

IV. High-Throughput Screening of Arrays of Metals and Chiral Ligands

As discussed in the Introduction, the choice of an appropriate chiral ligand or catalyst for an asymmetric transformation is often the result of knowledge-based intuition or serendipity and is normally followed by extensive trial and error optimization of a

Scheme 57

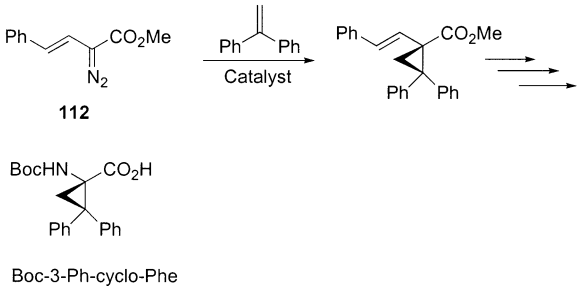


number of concurrent factors (ligand structure, metal ion, stoichiometry, solvent, temperature, etc.). In particular, a high-throughput screening approach involving arrays of chiral ligands with related (phosphines or diphosphines, oxazolines, amines, or diamines, etc.) or unrelated (miscellaneous ligands with different donor atoms) structures and different metal ions has been used to improve the enantioselectivity of several reactions.

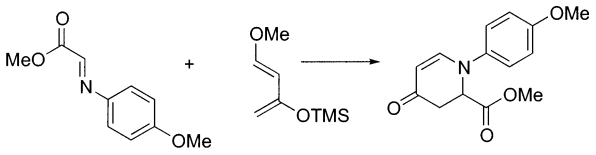
This approach has been used by Burgess and coworkers in 1996 for the identification of an effective catalyst for the formation of indolyl derivatives by intramolecular cyclization of diazoester **110** (Scheme 57).[143] This kind of reaction is known to proceed via carbene intermediates and is catalyzed by Rh(II) as well as by other metal ions. A set of five among the best known and effective ligands (two different bis-oxazolines, a pybox ligand, sparteine, and a chiral salen-type ligand) were reacted together with seven different metal ions [$AgSbF_6$, $Sc(OTf)_3$, [Rh(nbd)]-BPh_4, $(CuOTf)_2{\cdot}C_6H_6$, $La(OTf)_3$, $Yb(OTf)_3$, $AuCl(SMe_2)$] in four different solvents (THF, MeCN, $CHCl_3$, toluene). This should build up a library of 140 members, but since some of the combinations were not taken into consideration, only 96 were screened using a microtiter-plate format and a HPLC instrument equipped with autosampler. The screening confirmed the superiority of the previously characterized copper complex with bis-oxazoline ligand **111** but revealed an unexpected higher de when the reaction was carried out in THF rather than chloroform. In addition, a powerful catalyst was obtained with the same ligand and silver hexafluoroantimoniate, which is rarely used in this kind of chemistry. In this specific case, diastereoselection was similar to the copper case and yields were higher.

A similar strategy was applied in the enantioselective cyclopropanation of 1,1-diphenylethene with diazoester **112**, used in the synthesis of 3-phenyl-2,3-methanophenylalanine ("3-phenyl-cyclo-Phe") (Scheme 58).[144] In this case, a grid of five ligands (three different bis-oxazolines, a pybox, and a semicorrine ligand), five metal sources {$AgSbF_6$, $(CuOTf)_2{\cdot}C_6H_6$, $[RuCl_2(p\text{-cymene})]_2$, $Sc(OTf)_3$, $Pd(CH_3CN)_2Cl_2$}, and two different Davies−McKervey Rh catalysts [Rh_2(*S*-TBSP), Rh_2(*S*-DOSP)] were screened in different solvents and with different metal−ligand combinations/ratios in 24 glass vials set in wells drilled in a cooled aluminum block (Figure 1). The analysis (chiral HPLC with autosampler) revealed the superiority of Davies−McKervey Rh catalysts (ee 97%, yield 88%), although moderate enantioselectivity

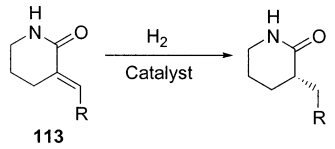
Scheme 58



Scheme 59



Scheme 60

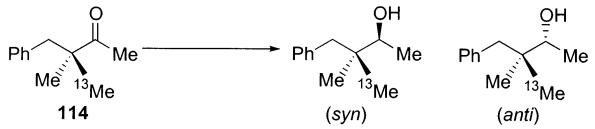


(65% ee) and yield (62%) could also be obtained with the combination of copper(I) triflate and a bisoxazoline.

A parallel approach to the identification of a chiral Lewis acid for the asymmetric aza-Diels−Alder reaction of an aryl glycine imine with Danishefsky's diene was reported by Whiting and co-workers (Scheme 59).[145] In particular, the parallel screening, which was run in solution using multiple well plates, involved initial examination of four different metal salts [Yb(OTf)$_3$, MgI$_2$, Cu(OTf)$_2$ FeCl$_3$], three different chiral ligands (*t*Bu$_2$-bisoxazoline, *R*-1,1′-binaphthol, *R,R*-1,2-diphenylethylenediamine) in three different solvents (CH_2Cl_2, toluene, CH_3CN) with two different additives (2,6-lutidine, 4Å-MS). Enantiomeric excesses (measured by chiral HPLC) as high as 97% were obtained with the combination MgI$_2$, *R,R*-1,2-diphenylethylenediamine, 2,6-lutidine in CH_3CN.

A high-throughput screening methodology for the identification of an effective catalyst for the enantioselective hydrogenation of 3-alkylidene-piperidone **113** was reported by Nugent and co-workers (Scheme 60).[146] A library of 32 chiral phosphines and 8 metal precursors was screened in 1-mL vials contained in 96 well plates and analyzed by chiral HPLC. The highest enantioselectivity (91% ee) was observed for the combination of 2,4-bis(diphenylphosphino)pentane (BDPP) and [(COD)$_2$Ir]BF_4 (COD = 1,5-cyclooctadiene). This result is quite unexpected since highly enantioselective ligands often possess a rigid skeleton, whereas in this case the DBPP backbone is highly flexible. An investigation of the substrate scope was then undertaken: hydrogenation of 3-alkylidene-2-piperidones containing either aromatic or aliphatic groups gave ee's consistently higher than 81%. Good enantioselectivities (75−89% ee) were also obtained for the analogous five- and seven-membered lactams.

Scheme 61



An array of 30 metal−ligand combinations for the transfer hydrogenation of dialkyl ketones was described by Morken and co-workers.[147] In this case, 10 different ligands (comprising seven amino alcohols, two amino acids, and *S*-prolinamide) and three different ruthenium(II) complexes {[$RuCl_2$(*p*-cymene)]$_2$, [$RuCl_2(C_6H_6)]_2$, [$RuCl_2(C_6Me_6)]_2$} were screened for the transfer hydrogenation (KOH/*i*PrOH as hydrogen source) of the enantioenriched isotopically chiral ketone **114** (Scheme 61). This substrate was obtained in 69% ee in gram quantities through a short synthetic sequence and used in a ^{13}C NMR assay for the determination of the enantiomeric excess. The assay is based on the fact that the two enantiotopic Me groups of **114** become diastereotopic and therefore anisochronous when the transfer hydrogenation takes place with generation of the second stereocenter. In addition, assuming that kinetic isotope effects are minimal, the integration of the ^{13}C-labeled Me signals of the two diastereomers (syn and anti) reflects the enantioselectivity of the asymmetric transformation, once the correction for the enantiomeric purity of ketone **114** (69% ee) has been applied. The analysis was performed directly on the reaction mixture, without quenching, by single-pulse, unlocked, unshimmed, nonspinning ^{13}C NMR, requiring about 15 s per acquisition. A comparison of ee determination using this NMR technique and conventional chiral GC revealed an average error of about ±3% in the ee value. The best enantioselectivities measured for the transfer hydrogenation (81% ee) were obtained with a combination of phenylglycinol and [$RuCl_2(C_6Me_6)]_2$. Besides the good enantioselectivities attained in the library screening, this paper describes a simple method for high-throughput screening of asymmetric reactions that uses standard instrumentation.

Another original high-throughput screening assay for the determination of both enantiomeric excess and yields was reported by Wagner, Mioskowsky, and coworkers, based on a competitive enzyme immunoassay (EIA).[56] The reaction chosen to test this assay was the asymmetric reduction of benzoylformic (BF) to mandelic acid (MA) by transfer hydrogenation. The catalyst library was prepared by combining a set of 22 chiral diamines (comprising four different scaffolds), 4 metal precursors, and 2 hydrogen sources (Scheme 62, Table 1). The assay was based on the highly specific binding properties of antibodies which allow for direct measurement of the concentration of a given product in complex mixtures. Thus, by using a monoclonal antibody that binds equally well both enantiomers of the product (MA), the yield of the reactions could be evaluated, whereas employing a monoclonal antibody which shows a high affinity for only one enantiomer of MA, the concentration of this enantiomer and therefore the enantioselectivity of the reaction could be evaluated. In practice, the crude catalyzed reaction mixture and a product−enzyme

Scheme 62

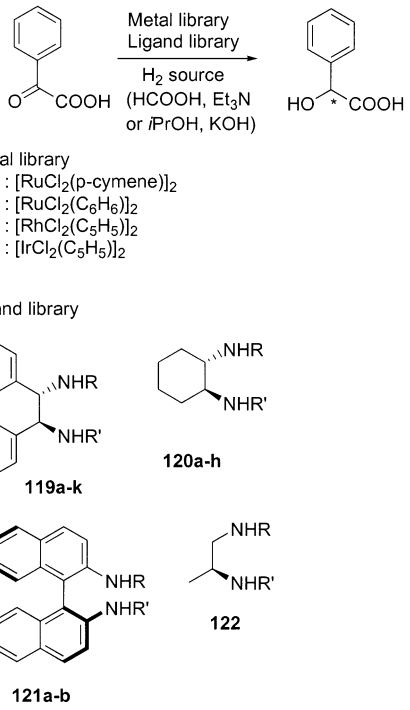


Table 1

L	R	R′
119a	H	H
119b	CF_3SO_2	H
119c	$C_4F_9SO_2$	H
119d	4-$CF_3C_6H_4SO_2$	H
119e	2,4,6-$(CH_3)_3C_6H_2SO_2$	H
119f	4-$CH_3C_6H_4SO_2$	H
119g	$C_6F_5SO_2$	H
119h	CF_3CO	H
119i	C_6H_5CO	H
119j	4-$CH_3C_6H_4SO_2$	4-$CH_3C_6H_4SO_2$
119k	$C_6H_5CH_2OCO$	$C_6H_5CH_2OCO$
120a	H	H
120b	CF_3SO_2	H
120c	$C_4F_9SO_2$	H
120d	4-$CH_3C_6H_4SO_2$	H
120e	2,4,6-$(CH_3)_3C_6H_2SO_2$	H
120f	4-$CF_3C_6H_4SO_2$	H
120g	CF_3SO_2	CF_3SO_2
120h	CH_3SO_2	CH_3SO_2
121a	H	H
121b	CF_3SO_2	H
122	H	H

conjugate were added to a 96-well microtiter plate containing a specific anti-product antibody immobilized on the solid phase. Catalytic activity results in the formation of a product that competes with the enzyme−product conjugate for antibody binding sites. This leads to a decrease in absorbance (signal related to the solid-phase-bound enzyme activity), which is related to the concentration of product in the reaction mixture. Monoclonal antibodies (mAbs) raised against hapten H3 (a vanillin mandelic acid analogue), which tightly bind a broad range of molecules with a MA moiety, were used for enantioselective binding. One hundered seventy six different reactions were screened in a few hours using this method.

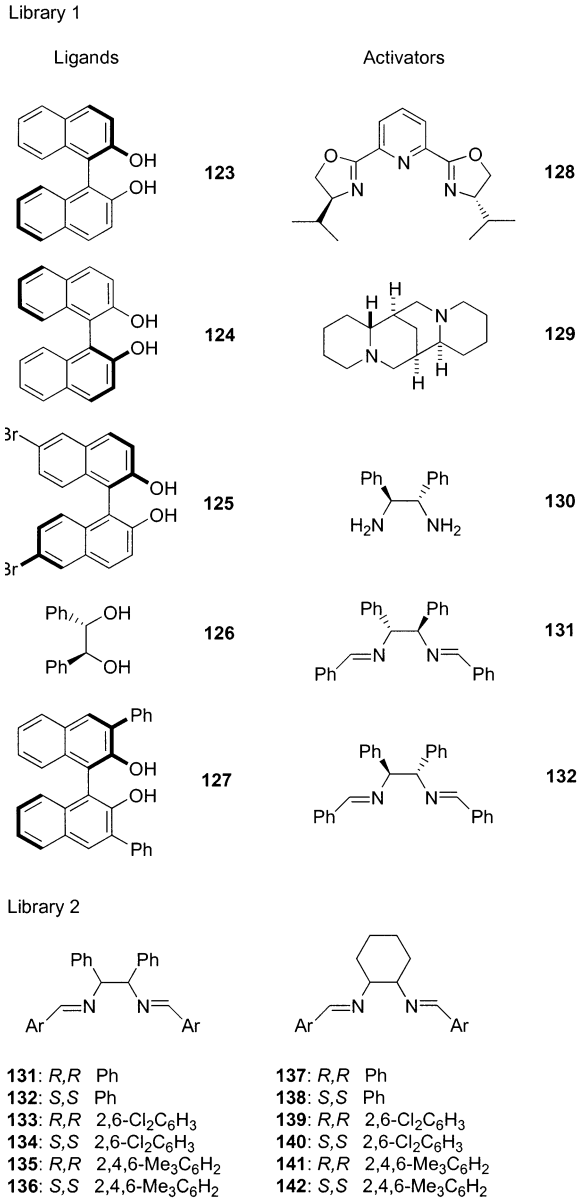
A comparison of the ee's values determined by EIA and by chiral HPLC on 42 representative samples from the crude catalyzed reactions was also performed. Good correlation was obtained for EIA and HPLC analysis (the precision of the ee determination was evaluated at ±9%). The screening of the library revealed that the best combination was as follows: *N*-trifluoromethylsulfonyl *S,S*-1,2-diphenylethylenediamine (**119b**), $[RuCl_2(p\text{-cymene})]_2$ (**115**), and HCOOH/TEA as hydrogen source in DMF (79−81% ee).

V. Parallel Libraries Resulting from Combinations of Chiral/Achiral Metal−Ligands and Additives

The "asymmetric amplification", "chiral poisoning", "asymmetric activation", and "asymmetric deactivation" strategies[148,149] take advantage of the aggregation phenomena among different ligands (chiral and achiral), additives, and metal ions [see also the contributions in this special issue of *Chemical Reviews* by (a) J. Faller, A. Lavoie, J. Parr; (b) K. Mikami; (c) P. J. Walsh]. These strategies seem very well suited for a combinatorial approach, where the active catalyst self-assembles in the reaction medium from dynamic combinatorial libraries of different ligand−metal−additive complexes.

Mikami and co-workers reported a super high-throughput screening (SHTS) of chiral ligands and activators; the asymmetric activation of chiral diol−zinc catalysts by chiral nitrogen activators was exploited in the enantioselective addition of diethylzinc to aldehydes.[41,43] The SHTS consists of a detection system based on the application of circular dichroism (CD) to HPLC on nonchiral stationary phases. The method allows the simultaneous monitoring of the CD signal $\Delta\epsilon$, the absorption ϵ, and their ratio $g = \Delta\epsilon/\epsilon$. The dissymmetry factor g is independent of concentration and is linearly related to the enantiomeric excess. With this technique, both the yield and the enantiomeric excess of the product could be determined within minutes without separation of the enantiomeric products. A small library of five different chiral diol ligands (**123**−**127**, Scheme 63) and five chiral activators (diamines or diimines, **128**−**132**) was screened for the Et_2Zn addition to benzaldehyde with the expectation that the combination of a diol and a chelating dinitrogen ligand would form a monomeric zinc complex. Enantioselectivity of the reaction was increased by matched combination of diol ligands and nitrogen activators. For example, **123** and **131** promoted the reaction to give (*S*)-1-phenylpropanol with 8.2% ee (54% yield) and 1.1% ee (64% yield), respectively. However, the combined use of **123** and **131** quantitatively provided the product with 37.4% ee (*S*). The best combinations were found to be **127**/**131** and **127**/**132** to provide (*S*)-1-phenylpropanol with up to 65% ee and in quantitative yields. A new library of diimine activators (**131**−**142**) was then prepared by simple condensation of enantiopure 1,2-diphenylethylenediamine or 1,2-diamino cyclohexane with 2 equiv of aromatic aldehydes. The best combination found was **127**/**136**, which was further optimized by lowering the reaction temperature to −78 °C (99% ee, quantitative yield).

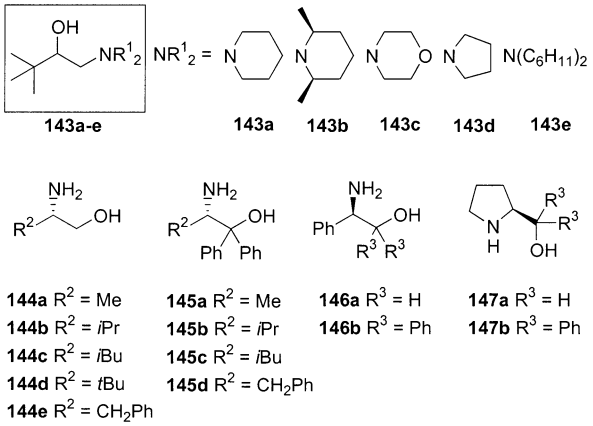
Scheme 63



The use of a small library of chiral diamine activators (4) was also reported by Mikami and co-workers in combination with the achiral ligand diphenylphosphinoferrocene to form enantiomerically and diastereomerically pure mixed diamine−diphosphine nickel complexes.[150] These complexes were then used in the asymmetric catalysis of the glyoxylate−ene reaction with ee's as high as 92%.

A highly enantioselective addition of Et_2Zn to aldehydes catalyzed by a combination of racemic amino alcohols and chiral, enantiopure additives was reported by Ding and co-workers.[151] This approach consists of the addition of a chiral, enantiopure additive to a racemic catalyst system in order to enantioselectively generate a new metal complex involving the chiral additive and one enantiomer of the racemic ligand, thus leaving the other enantiomer free for asymmetric catalysis. A library of five racemic amino alcohols (**143a**−**e**, Scheme 64, "the racemic ligands") and a library of 13 optically pure amino alcohols (**144**−**147**, "the chiral additives") were prepared. The combined use of 10 mol % of the racemic

Scheme 64

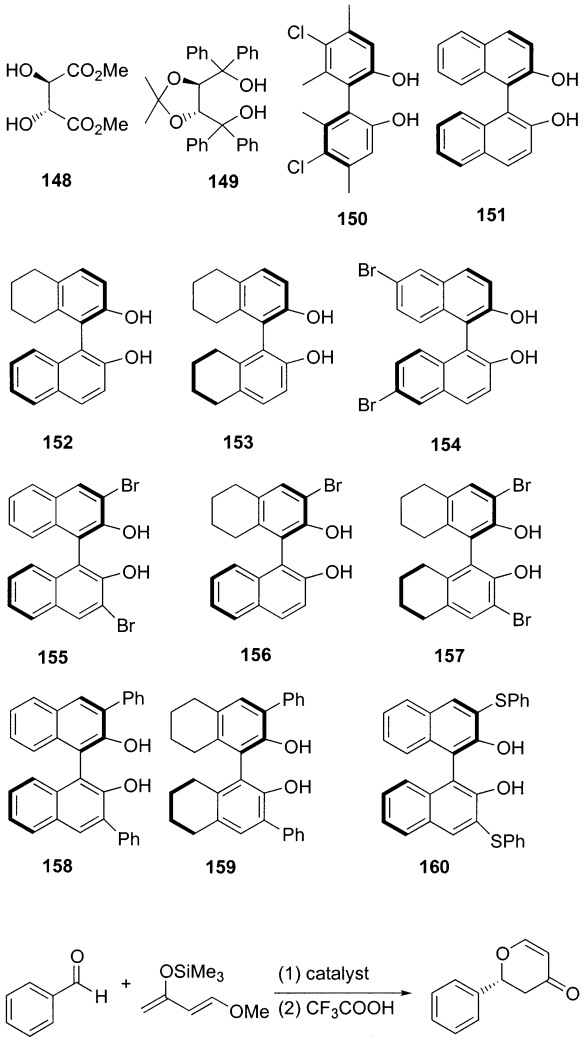


amino alcohols (**143a**−**e**) and 5 mol % of the optically pure additives (**144**−**147**) in the presence of Et_2Zn formed a chiral catalyst library of 65 members, which were then screened for the diethylzinc addition to benzaldehyde and analyzed with the HPLC−CD technique described above.[41,43] The reactions catalyzed by the best combinations were further optimized in parallel by varying the molar ratio of racemic ligand to chiral additive and decreasing the reaction temperature to −40 °C. Eventually (*S*)-1-phenylpropanol was obtained in 93% ee and >95% yield under the catalysis of **147b** (5 mol %)/**143a** (10 mol %).

Ding and co-workers also described the development of highly efficient enantioselective catalysts for the hetero Diels−Alder (HDA) reaction of Danishefsky's diene with benzaldehyde by high-throughput screening of a combinatorial library of chiral titanium complexes (Scheme 65).[152] The library was obtained starting from an array of 13 chiral diols (**148**−**160**) by in situ parallel combination of a diol ligand ($\mathbf{L_{148-160}}$) with Ti(O*i*Pr)$_4$ and a second diol ligand ($\mathbf{L_{148-160}}$). The authors state "Every member of the $\mathbf{L_m/Ti/L_n}$ library is actually a mixture of titanium complexes because of ligand diversity and the aggregation feature of titanium complexes. These molecular assemblies form spontaneously, and the composition of the mixtures depends on thermodynamic factors. Therefore, the *in situ* selection of a highly reactive (and selective) metallic complex from a variety of thermodynamically dictated assemblies by substrate will lead to the highly enantioselective asymmetric catalysis". The best combinations identified from the screening were **152**/**Ti**/**152** and **152**/**Ti**/**153**, which afforded the HDA reaction product in very good yield (>99% and 82%, respectively) and excellent enantiomeric excess (>99%), running the reaction at room temperature, in the absence of solvent, and with exceptionally low catalyst loadings (0.1−0.005 mol %).

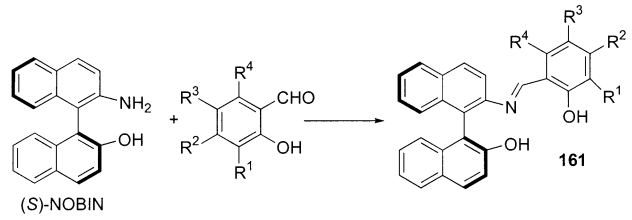
In a subsequent paper, Ding and co-workers described the successful development of a group of highly efficient chiral tridentate titanium catalysts for the hetero Diels−Alder (HDA) reaction of Danishefsky's diene with a variety of aldehydes through ligand and additive diversity.[153] A library of 22 tridentate Schiff-base ligands **161** was prepared from the condensation of (*S*)-2-amino-2′-hydroxy-1,1′-bi-

Scheme 65

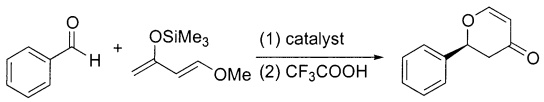


naphthyl (*S*-NOBIN) with a variety of differently substituted salicylaldehydes by parallel solution-phase synthesis in 59−99% yields (Scheme 66). After the serendipitous discovery that the presence of 5% benzoic acid and 4 Å MS dramatically improved the activity and selectivity of the titanium/**161a** complex in the HDA reaction, the library of ligands **161a**−**v** was screened in the presence of benzoic acid and 4 Å MS (with a molar ratio of **161**/Ti(O*i*Pr)$_4$/PhCOOH/benzaldehyde = 0.2/0.1/0.05/1). The best results (ee = 85−91%) were obtained using ligands **161a**, **161e**, **161h**, and **161m** which displayed a reduced steric hindrance at the *ortho*-position of the phenol group. A library of 36 carboxylic acid additives, including aromatic, aliphatic, salicylic, and amino acids, was then screened to improve the enantioselectivity of the **161a**/Ti-catalyzed HDA reaction. While achiral carboxylic acids could improve the enantioselectivity in many cases, the best additive turned out to be a chiral carboxylic acid, (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid (Naproxen), which promoted the reaction with a quantitative yield and 97% ee of the product (*S*). The scope of the reaction was then investigated on several aldehyde substrates, both aromatic and aliphatic, using ligands **161a** and **161e**−**h** in combination with Naproxen as an additive, in toluene, in the presence of 4 Å MS, at room

Scheme 66



161a; $R^1 = R^2 = R^3 = R^4 = H$
161b; $R^1 = R^3 = Cl$, $R^2 = R^4 = H$
161c; $R^1 = R^3 = Br$, $R^2 = R^4 = H$
161d; $R^1 = R^3 = I$, $R^2 = R^4 = H$
161e; $R^3 = F$, $R^1 = R^2 = R^4 = H$
161f; $R^3 = Cl$, $R^1 = R^2 = R^4 = H$
161g; $R^3 = Br$, $R^1 = R^2 = R^4 = H$
161h; $R^3 = I$, $R^1 = R^2 = R^4 = H$
161i; $R^1 = OCH_3$, $R^2 = R^3 = R^4 = H$
161j; $R^2 = OCH_3$, $R^1 = R^3 = R^4 = H$
161k; $R^3 = OCH_3$, $R^1 = R^2 = R^4 = H$
161l; $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$
161m; $R^3 = CH_3$, $R^1 = R^2 = R^4 = H$
161n; $R^1 = t$Bu, $R^2 = R^3 = R^4 = H$
161o; $R^3 = t$Bu, $R^1 = R^2 = R^4 = H$
161p; $R^1 = R^3 = t$Bu, $R^2 = R^4 = H$
161q; $R^1 = t$Bu, $R^3 = CH_3$, $R^2 = R^4 = H$
161r; $R^1 = Br$, $R^3 = CH_3$, $R^2 = R^4 = H$
161s; $R^1 = Br$, $R^3 = OCH_3$, $R^2 = R^4 = H$
161t; $R^1 = Br$, $R^3 = t$Bu, $R^2 = R^4 = H$
161u; $R^1 = OCH_3$, $R^3 = Br$, $R^2 = R^4 = H$
161v; R^3-R^4 = -$(CH)_4$-, $R^1 = R^2 = H$

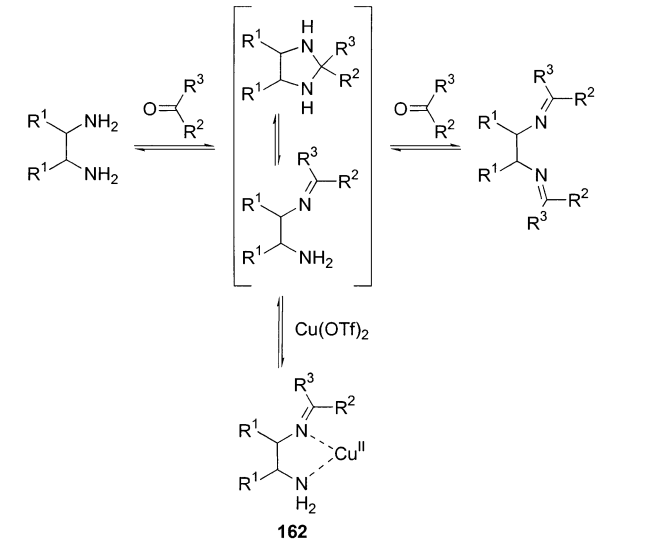


temperature. Good to excellent enantioselectivities and yields were obtained for all the substrates. From a mechanistic point of view, when racemic **161a** (10 mol %) was employed in the presence of 5% mol Naproxen, the HDA product (aldehyde = benzaldehyde) was obtained in 70% yield and 55% ee (*S*). This result clearly shows that Naproxen is able to activate selectively the (*S*)-enantiomer of the racemic **161a**/Ti complex.

A simple methodology for the generation of three-component chiral complexes **162** from easily available starting materials was described by Dalko, Cossy, and co-workers (Scheme 67).[154] A small library of 10 chiral ligands was prepared by condensation of a chiral diamine [(*R*,*R*)- and (*S*,*S*)-1,2-diphenylethylenediamine, (*R*,*R*)-1,2-diamino cyclohexane] with a ketone [cyclohexanone, cyclopentanone, cyclobutanone, (−)-menthone, acetone] or an aldehyde (benzaldehyde) in a 1:1 molar ratio. Complexes **162** were then formed by adding a stoichiometric amount of $Cu(OTf)_2$ to the reaction mixtures and allowing them to stand at room temperature for 16 h. This premixing time significantly influenced the enantioselectivity of the subsequent reaction. Complexes **162** (10 mol %) were then screened in the condensation between Danishefsky's diene and ethyl piruvate to form the dihydropyrone HDA adduct in up to 85% yield and 94% enantiomeric excess [with complex **162** formed from (*S*,*S*)-1,2-diphenylethylenediamine and cyclobutanone].

The asymmetric borane reduction of acetophenone using mixtures of homochiral β-amino alcohol ligands was investigated by Kaptein, Broxterman, and co-workers at DSM-research (Geleen).[155] Four amino alcohols were used: (*S*)-phenylglycinol, (1*S*,2*R*)-1-amino-2-indanol, (1*R*,2*S*)-norephedrine, and (*S*)-prolinol. With stoichiometric amounts of a mixture of two- or three-amino alcohols, the ee remained at the level of the best amino alcohol [(1*S*,2*R*)-1-amino-2-

Scheme 67



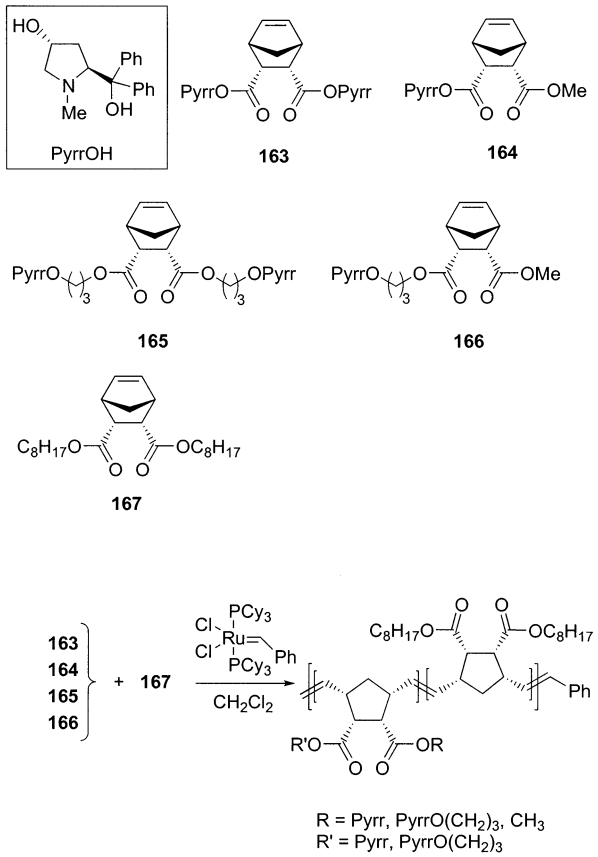
indanol, ee = 80−84%] for a wide composition range. When using a catalytic amount of amino alcohols as ligands, a small but statistically significant enhancement in ee (+5% ee) was observed when a mixture of 5% (1*S*,2*R*)-1-amino-2-indanol and 5% (*S*)-phenylglycinol was used as chiral ligand, compared to the separate 10% amino alcohols (20% ee in both cases). Under these conditions ee's are rather low due to the concurrent uncatalyzed reaction. The fact that the ee in the asymmetric borane reduction using mixtures of chiral ligands is almost equal to the ee provided the best ligand in the mixture offers the opportunity for a fast and efficient screening method.

VI. Chiral Ligands with Undetermined Structure

In the preceding sections we have discussed catalytic systems of known composition, although not always of known structure. From a pragmatic point of view (i.e., the function is important not the structure, see the Introduction of this review for a detailed discussion of this concept),[22,23] catalytic systems of undetermined structure could be used provided that good enantioselectivities are attained for the reaction of interest.

The only example of this promising strategy has been developed by Bolm and co-workers, who reported the synthesis of highly functionalized chiral polymers by ring-opening metathesis polymerization (ROMP) of norbornenes bearing catalytically active prolinol-type units (**163**−**166**, Scheme 68).[24] In a highly modular approach, the properties of the polymers could be modified by random copolymerization with catalytically inactive achiral monomer **167**. By changing the achiral-to-chiral monomer ratio, a large number of such copolymers was obtained, each having its own unique distribution of catalyti-

Scheme 68



cally active sites along the polymer chain. Treatment of binary mixtures of the four chiral monomers **163**−**166** and achiral monomer **167** in six different ratios (chiral monomer/**167** = 100:0 to 11:89) with Grubbs' ROMP catalyst (10 mol %) in dichloromethane afforded 24 different macromolecules resulting from homo- and random copolymerizations. The resulting polymers had high molecular weight and were soluble in organic solvents, such as toluene. The 24 polymers were then tested in parallel as catalysts in the addition of diethylzinc to benzaldehyde, and the enantioselectivities were checked by chiral HPLC after purification. The highest enantiomeric excesses were obtained from random copolymers derived from 1:1 mixtures of the chiral and achiral monomers [in particular, **163**/**167** (1:1) and **164**/**167** (1:1) gave 87% ee; **166**/**167** (1:1) gave 89% ee]. It is interesting to note that the ee values achieved with the optimal polymers were significantly higher than those obtained with the corresponding monomers (e.g., **163**, ee 72%; **164**, ee 71%). It is clear that the polymer backbone in not simply playing the role of support for the catalytically active sites but actively participates to the creation of chiral "microenvironments, which provided excellent geometrical orientations for achieving high enantioselectivities". It was also shown that the stereogenic centers in the polymer backbone and their mutual interplay have a major impact on the microenvironment along the polymer chain. The strategy described in this work (the polymer itself is part of the chiral ligand and is optimized for a given reaction) greatly differs from the resin-bound version of well-known and effective homogeneous catalysts, which have often met with deceiving results, and

constitutes a new approach to the synthesis of enantioselective polymeric catalysts.

VII. Conclusions

As noted by Nobel laureate William Knowles in his 1983 review article:[156] "Since achieving 95% ee only involves energy differences of about 2 kcal, which is no more than the barrier encountered in a simple rotation of ethane, it is unlikely that before the fact one can predict what kind of ligand structures will be effective." With Knowles, we look forward to the time when computational methods and mechanistic knowledge will permit the prediction of the optimum catalyst for new applications. Until that day, combinatorial methodologies will remain an invaluable tool for catalyst discovery and optimization.

After the completion of the present review article, a number of papers appeared in the 2003 literature which are relevant to this subject.[157−171]

VIII. Acknowledgments

We thank the European Commission (IHP Network grant HPRN-CT-2000-00014 "The Discovery of New Catalysts through Combinatorial Chemistry: Activity and Selectivity from Diversity") and Merck Research Laboratories (Merck's Academic Development Program Award to C. Gennari, 2002) for financial support. U. Piarulli thanks the Dipartimento di Chimica Organica e Industriale of Milan University for their hospitality.

IX. References

(1) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998−2007.
(2) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008−2023.
(3) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024−2032.
(4) Gennari, C.; Nestler, H. P.; Piarulli, U.; Salom, B. *Liebigs Ann.-Recl.* **1997**, 637−647.
(5) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885−1889.
(6) Hoveyda, A. H. *Chem. Biol.* **1998**, *5*, R187−R191.
(7) Jandeleit, B.; Weinberg, W. H. *Chem. Ind.* **1998**, 795−798.
(8) Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2495−2532.
(9) Dahmen, S.; Bräse, S. *Synthesis* **2001**, 1431−1449.
(10) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284−310.
(11) Reetz, M. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1335−1338.
(12) Gilbertson, S. R. In *Progress in Inorganic Chemistry*; Carlin, K., Ed.; Wiley: New York, 2001; Vol. 50.
(13) de Vries, J. G.; de Vries, A. H. M. *Eur. J. Org. Chem.* **2003**, 799−811.
(14) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113−126.
(15) Landis, C. R.; Halpern J. *J. Am. Chem. Soc.* **1987**, *109*, 1746−1754.
(16) Brown, J. M.; Chaloner, P. A. *J. Am. Chem. Soc.* **1980**, *102*, 3040−3048.
(17) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357.
(18) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877−7878.
(19) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036.
(20) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800−9809.
(21) Buono, F.; Walsh, P. J.; Blackmond D. G. *J. Am. Chem. Soc.* **2002**, *124*, 13652−13653.
(22) Menger, F. M.; Eliseev, A. V.; Migulin, V. A. *J. Org. Chem.* **1995**, *60*, 6666−6667.
(23) Menger, F. M.; Ding, J.; Barragan, V. *J. Org. Chem.* **1998**, *63*, 7578−7579.
(24) Bolm, C.; Tanyeli, C.; Grenz, A.; Dinter, C. L. *Adv. Synth. Catal.* **2002**, *344*, 649−656.
(25) Liebeton, K.; Zonta, A.; Schimossek, K.; Nardini, M.; Lang, D.; Dijkstra, B. W.; Reetz, M. T.; Jaeger, K. E. *Chem. Biol.* **2000**, *7*, 709−718.
(26) Reetz, M. T.; Jaeger, K. E. *Chem. Eur. J.* **2000**, *6*, 407−412.
(27) Reetz, M. T.; Wilensek, S.; Zha, D. X.; Jaeger, K. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3589−3591.
(28) Reetz, M. T. *Tetrahedron* **2002**, *58*, 6595−6602.
(29) DeSantis, G.; Zhu, Z. L.; Greenberg, W. A.; Wong, K. V.; Chaplin, J.; Hanson, S. R.; Farwell, B.; Nicholson, L. W.; Rand, C. L.; Weiner, D. P.; Robertson, D. E.; Burk, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9024−9025.
(30) Reetz, M T.; Zonta, A.; Schimossek, K.; Liebeton, K.; Jaeger, K.-E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2830−2832.
(31) Janes, L. E.; Kazlauskas, R. J. *J. Org. Chem.* **1997**, *62*, 4560−4561.
(32) Reetz, M. T.; Becker, M. H.; Klein, H. W.; Stockigt, D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1758−1761.
(33) Schrader, W.; Eipper, A.; Pugh, D. J.; Reetz, M. T. *Can. J. Chem.* **2002**, *80*, 626−632.
(34) Reetz, M. T.; Eipper, A.; Tielmann, P.; Mynott, R. *Adv. Synth. Catal.* **2002**, *344*, 1008−1016.
(35) Guo, J. H.; Wu, J. Y.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1755−1758.
(36) Reetz, M. T.; Becker, M. H.; Kuhling, K. M.; Holzwarth, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2647−2650.
(37) Reetz, M. T.; Hermes, M.; Becker, M. H. *Appl. Microbiol. Biotechnol.* **2001**, *55*, 531−536.
(38) Reetz, M. T.; Kühling, K. M.; Deege, A.; Hinrichs, H.; Belder, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 3891−3893.
(39) Reetz, M. T.; Kühling, K. M.; Wilensek, S.; Husmann, H.; Häusig, U. W.; Hermes, M. *Catal. Today* **2001**, *67*, 389−396.
(40) Reetz, M. T.; Kühling, K. M.; Hinrichs, H.; Deege, A. *Chirality* **2000**, *12*, 479−482.
(41) Ding, K. L.; Ishii, A.; Mikami, K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 497−501.
(42) Angelaud, R.; Matsumoto, Y.; Korenaga, T.; Kudo, K.; Senda, M.; Mikami, K. *Chirality* **2000**, *12*, 544−547.
(43) Mikami, K.; Angelaud, R.; Ding, K. L.; Ishii, A.; Tanaka, A.; Sawada, N.; Kudo, K.; Senda, M. *Chem. Eur. J.* **2001**, *7*, 730−737.
(44) Hattori, T.; Minato, Y.; Yao, S.; Finn, M. G.; Miyano, S. *Tetrahedron Lett.* **2001**, *42*, 8015−8018.
(45) Pugh, V. J.; Hu, Q. S.; Pu, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3638−3641.
(46) Pugh, V. J.; Hu, Q. S.; Zuo, X. B.; Lewis, F. D.; Pu, L. *J. Org. Chem.* **2001**, *66*, 6136−6140.
(47) Lin, J.; Zhang, H.-C.; Pu, L. *Org. Lett.* **2002**, *4*, 3297−3300.
(48) Reetz, M. T.; Sostmann, S. *Tetrahedron* **2001**, *57*, 2515−2520.
(49) Kubo, Y.; Maeda, S.; Tokida, S.; Kubo, M. *Nature* **1996**, *382*, 522−524.
(50) van Delden, R. A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3198−3200.
(51) van Delden, R. A.; Feringa, B. L. *Chem. Commun.* **2002**, 174−175.
(52) Janes, L. E.; Löwendahl, A. C.; Kazlauskas, R. J. *Chem. Eur. J.* **1998**, *4*, 2324−2331.
(53) Morìs-Varas, F.; Shah, A.; Aikens, J.; Nadkarni, N. P.; Rozzell, J. D.; Demirjian, D. C. *Biorg. Med. Chem.* **1999**, *7*, 2183-2188.
(54) Yan, Y.; Myrick, M. L. *Anal. Chem.* **1999**, *71*, 1958−1962.
(55) Chen, Y.; Shimizu, K. D. *Org. Lett.* **2002**, *4*, 2937−2940.
(56) Taran, F.; Gauchet, C.; Mohar, B.; Meunier, S.; Valleix, A.; Renard, P. Y.; Creminon, C.; Grassi, J.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 124−127.
(57) Abato, P.; Seto, C. T. *J. Am. Chem. Soc.* **2001**, *123*, 9206−9207.
(58) Baumann, M.; Stürmer, R.; Bornscheuer, U. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 4201−4204.
(59) Klein, G.; Reymond, J. L. *Helv. Chim. Acta* **1999**, *82*, 400−407.
(60) Korbel, G. A.; Lalic, G.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 361−362.
(61) Liu, G. C.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712−7713.
(62) Gilbertson, S. R.; Wang, X. F. *Tetrahedron Lett.* **1996**, *37*, 6475−6478.
(63) Gilbertson, S. R.; Wang, X. F. *Tetrahedron* **1999**, *55*, 11609−11618.
(64) Gilbertson, S. R.; Collibee, S. E.; Agarkov, A. *J. Am. Chem. Soc.* **2000**, *122*, 6522−6523.
(65) Gilbertson, S. R.; Chang, C. W. T. *Chem. Commun.* **1997**, 975−976.
(66) Gilbertson, S. R.; Chang, C. W. T. *J. Org. Chem.* **1998**, *63*, 8424−8431.
(67) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237−2240.
(68) Xu, G. P.; Gilbertson, S. R. *Tetrahedron Lett.* **2002**, *43*, 2811−2814.
(69) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668−1671.
(70) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704−1707.

(71) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284−4285.
(72) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657−2658.
(73) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009−1012.
(74) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984−985.
(75) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756.
(76) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781.
(77) Luchaco-Cullis, C. A.; Hoveyda, A. H.*J. Am. Chem. Soc.* **2002**, *124*, 8192−8193.
(78) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363.
(79) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456−1460.
(80) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C.; Jackson, R. F. W. *J. Org. Chem.* **1998**, *63*, 5312−5313.
(81) Kagan, H. B. *J. Organomet. Chem.* **1998**, *567*, 3−6.
(82) Gao, X.; Kagan, H. B. *Chirality* **1998**, *10*, 120−124.
(83) Brouwer, A. J.; van der Linden, H. J.; Liskamp, R. M. J. *J. Org. Chem.* **2000**, *65*, 1750−1757.
(84) Wolf, C.; Hawes, P. A. *J. Org. Chem.* **2002**, *67*, 2727−2729.
(85) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773−5778.
(86) Chataigner, I.; Gennari, C.; Piarulli, U.; Ceccarelli, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 916−918.
(87) Chataigner, I.; Gennari, C.; Ongeri, S.; Piarulli, U.; Ceccarelli, S. *Chem. Eur. J.* **2001**, *7*, 2628−2634.
(88) Ongeri, S.; Piarulli, U.; Jackson, R. F. W.; Gennari, C. *Eur. J. Org. Chem.* **2001**, 803−807.
(89) Ongeri, S.; Piarulli, U.; Roux, M.; Monti, C.; Gennari, C. *Helv. Chim. Acta* **2002**, *85*, 3388−3399.
(90) Only one-half (14) of the full matrix of all the possible different ligands (i.e., $7 \times 4 = 28$) was prepared, following a sort of "positional scanning" approach.
(91) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 234−236.
(92) Balsells, J.; Mejorado, L.; Phillips, M.; Ortega, F.; Aguirre, G.; Somanathan, R.; Walsh, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 4135−4142.
(93) Balsells, J.; Walsh, P. J. *J. Org. Chem.* **2000**, *65*, 5005−5008.
(94) Green, S. D.; Monti, C.; Jackson, R. F. W.; Anson, M. S.; Macdonald, S. J. F. *Chem. Commun.* **2001**, 2594−2595.
(95) Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2640−2642.
(96) Pelotier, B.; Anson, M. S.; Campbell, I. B.; MacDonald, S. J. F.; Priem, G.; Jackson, R. F. W. *Synlett* **2002**, 1055−1060.
(97) Lake, F.; Moberg, C. *Eur. J. Org. Chem.* **2002**, 3179−3188.
(98) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180−9187.
(99) Boger, D. L.; Brotherton C. E. *J. Org. Chem.* **1984**, *49*, 4050−4055.
(100) Burgess, K.; Porte, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 2465−2469.
(101) Hou, D. R.; Burgess, K. *Org. Lett.* **1999**, *1*, 1745−1747.
(102) Hou, D. R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206−215.
(103) Hou, D. R.; Reibenspies, J.; Colacot, T. J.; Burgess, K. *Chem. Eur. J.* **2001**, *7*, 5391−5400.
(104) Kranich, R.; Eis, K.; Geis, O.; Muhle, S.; Bats, J. W.; Schmalz, H. G. *Chem. Eur. J.* **2000**, *6*, 2874−2894.
(105) Blume, F.; Zemolka, S.; Fey, T.; Kranich, R.; Schmalz, H. G. *Adv. Synth. Catal.* **2002**, *344*, 868−883.
(106) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem. Commun.* **2002**, 673−675.
(107) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem. Eur. J.* **2002**, *8*, 4767−4780.
(108) Huttenloch, O.; Spieler, J.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 671−675.
(109) Altava, B.; Burguete, M. I.; Garcia-Verdugo, E.; Luis, S. V.; Pozo, O.; Salvador, R. V. *Eur. J. Org. Chem.* **1999**, 2263−2267.
(110) Nugent, W. A.; Licini, G.; Bonchio, M.; Bortolini, O.; Finn, M. G.; McCleland, B. W. *Pure Appl. Chem.* **1998**, *70*, 1041−1046.
(111) Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119−3121.
(112) Pastó, M.; Riera, A.; Pericàs, M. A. *Eur. J. Org. Chem.* **2002**, 2337−2341.
(113) Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164−4178.
(114) Desimoni, G.; Faita, G.; Mella, M. *Tetrahedron* **1996**, *52*, 13649−13654
(115) Neuville, L.; Chastanet, J.; Zhu, J. P. *Tetrahedron Lett.* **1999**, *40*, 7087−7090.
(116) Matsuo, J.; Odashima, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 345−347.
(117) Kobayashi, S.; Kusakabe, K.-I.; Ishitani, H. *Org. Lett.* **2000** *2*, 1225−1227.
(118) Hoshino, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10452−10453.
(119) Christoffers, J.; Mann, A.; Pickardt, J. *Tetrahedron* **1999**, *55*, 5377−5388.
(120) Dyker, G.; Breitenstein, K.; Henkel, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1929−1936.
(121) Francis, M. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 937−941.
(122) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748.
(123) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481−2495.
(124) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901−4902.
(125) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279−1281.
(126) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867−870.
(127) Su, J. T.; Vachal, P.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 197−200.
(128) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012−10014.
(129) Wenzel, A. G.; Jacobsen, E. N.*J. Am. Chem. Soc.* **2002**, *124*, 12964−12965.
(130) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629−1630.
(131) Jarvo, E. R.; Vasbinder, M. M.; Miller, S. J. *Tetrahedron* **2000**, *56*, 9773−9779.
(132) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496−6502.
(133) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306−4307.
(134) Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522−5527.
(135) Papaioannou, N.; Evans, C. A.; Blank, J. T.; Miller, S. J. *Org. Lett.* **2001**, *3*, 2879−2882.
(136) Sculimbrene, B. R.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125−10126.
(137) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 11653−11656.
(138) Alvarez, R.; Hourdin, M. A.; Cave, C.; d'Angelo, J.; Chaminade, P. *Tetrahedron Lett.* **1999**, *40*, 7091−7094.
(139) Lygo, B.; Andrews, B. I.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **2002**, *43*, 8015−8018.
(140) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539−9543.
(141) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245−1248.
(142) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167−8177.
(143) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220−222.
(144) Moye-Sherman, D.; Welch, M. B.; Reibenspies, J.; Burgess, K. *Chem. Commun.* **1998**, 2377−2378.
(145) Bromidge, S.; Wilson, P. C.; Whiting, A. *Tetrahedron Lett.* **1998**, *39*, 8905−8908.
(146) Yue, T.-Y.; Nugent, W. A. *J. Am. Chem. Soc.* **2002**, *124*, 13692−13693.
(147) Evans, M. A.; Morken, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 9020−9021.
(148) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532−3556
(149) Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561−1578.
(150) Mikami, K.; Aikawa, K. *Org. Lett.* **2002**, *4*, 99−101.
(151) Long, J.; Ding, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 544−547.
(152) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10−11.
(153) Yuan, Y.; Long, J.; Sun, J.; Ding, K. *Chem. Eur. J.* **2002**, *8*, 5033−5042.
(154) Dalko, P. I.; Moisan, L.; Cossy, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 625−628.
(155) Kaptein, B.; Elsenberg, H.; Minnaard, A. J.; Broxterman, Q. B.; Hulshof, L. A.; Koek, J.; Vries, T. R. *Tetrahedron: Asymmetry* **1999**, *10*, 1413−1418.
(156) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.
(157) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113−123.
(158) Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3−10.
(159) Cobley, C. J.; Henschke J. P. *Adv. Synth. Catal.* **2003**, *345*, 195−201.
(160) Kawabata, T.; Stragies, R.; Fukaya, T.; Nagaoka, Y.; Schedel, H.; Fuji, K. *Tetrahedron Lett.* **2003**, *44*, 1545−1548.
(161) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 790−793.

(162) Burguete, M. I.; Collado, M.; Garcìa-Verdugo, E.; Vicent, M. J.; Luis, S. V.; Graf von Keyserling, N.; Martens, J. *Tetrahedron* **2003**, *59*, 1797−1804.
(163) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276−1279.
(164) Du, H.; Ding, K. *Org. Lett.* **2003**, *5*, 1091−1093.
(165) Yao, S.; Meng, J.-C.; Siuzdak, G.; Finn, M. G. *J. Org. Chem.* **2003**, *68*, 2540−2546.
(166) Papaioannou, N.; Blank, J. T.; Miller, S. J. *J. Org. Chem.* **2003**, *68*, 2728−2734.
(167) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018−4019.
(168) 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*, 1087−1089.
(169) Buck, R. T.; Coe, E. M.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *Tetrahedron: Asymmetry* **2003**, *14*, 791−816.
(170) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690−4691.
(171) Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, *68*, 3844−3848.

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