Design and Optimization of New Phosphine Oxazoline Ligands via High-Throughput Catalyst Screening

Alexander M. Porte, Joe Reibenspies, and Kevin Burgess*

Contribution from the Texas A & M University, Chemistry Department, P.O. Box 300012, College Station, Texas 77842

Received April 10, 1998

Abstract: This paper uses the phosphine oxazoline ligands **1** and an allylation transformation (reaction 1) to illustrate the value of divergent ligand syntheses and high-throughput screening in catalyst discovery and optimization. Thus, a diverse set of ligands **1** (Table 1) was prepared via a divergent synthesis involving the pivotal intermediate, phosphine-substituted amino alcohol **7** (Scheme 1). Single-crystal X-ray crystallographic data was obtained for a nickel complex **8** (Figure 3) of the phenyl-substituted ligand **1i**. This analysis illustrated some structural features of the ligand systems **1** that may be conducive to asymmetric catalysis. High-throughput screens were then used to correlate the ligand **1** R-substituents with asymmetric induction in the allylation reaction 1, and it emerged that the pseudo-spherical adamantyl substituent was superior to other R-substituents. Other parameters in the catalyst systems were also varied, sometimes in "two-dimensional" screens. No pronounced solvent effects were identified. Abstraction of chloride was shown to be detrimental, whereas addition of chloride provided no advantages. One of the most critical of all the variables probed was, rather surprisingly, the effect of ligand-to-metal ratio; enantioselectivities dropped sharply and eventually reversed when this ratio was increased above 1:1. These observations were rationalized in terms of a chelated complex **A** and a nonchelated one **B** (Scheme 3). The implications of these results for high-throughput screening of catalyst systems in general, and for ligands **1** in particular, are discussed.

Introduction

There are two extreme approaches to the task of preparing and testing chemical libraries (Figure 1). The classical one is via sequential methods, in a one-at-a-time fashion. This facilitates thorough quality control of samples entering the screen and careful policing of the assay so that accurate data are obtained. At the other extreme are truly combinatorial methods in which relatively large numbers of compounds are prepared in such a way that interesting products can be identified via a method which is facile relative to the complexity of the library. Examples of the latter approach include split and mix methodologies,[1−3] various applications of T-bags[4] including deconvolution of complex mixtures,[5] and libraries produced via photolithography.[6,7] These methods are much faster but allow for less control over the purity of the compounds entering the screen and the assay used.

Intermediate between the two extremes outlined above are methods based on parallel (or array) syntheses, usually in a one-compound-per-well format, coupled with automated screens. It is debatable whether these approaches are combinatorial, but they are certainly extremely useful. They facilitate higher levels of quality control than the more ambitious approaches to library syntheses and a significantly enhanced throughput relative to sequential methods. Consequently, parallel syntheses coupled with automated screens have become the focus of many ventures in the pharmaceutical industry.[8−11]

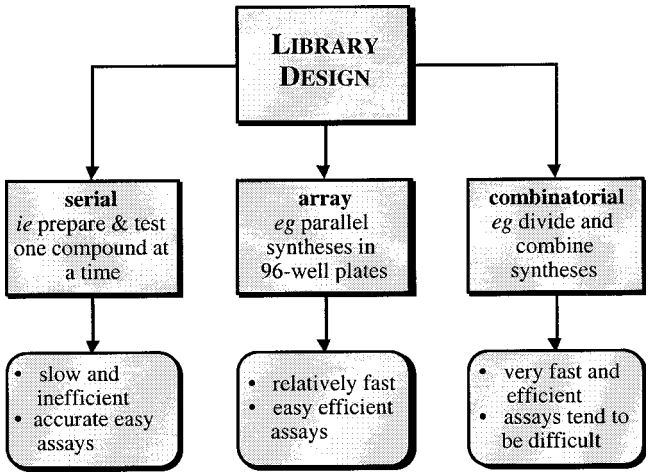


Figure 1. Conventional, array, and combinatorial approaches to synthesis and screening.

(1) Sebestyén, F.; Dibó, G.; Kovács, A.; Furka, A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 413.
(2) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82.
(3) Lam, K. S.; Hruby, V. J.; Lebl, M.; Knapp, R. J.; Kazmierski, W. M.; hersh, E. M.; Salmon, S. E. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 419.
(4) Houghten, R. A. *Proc. Natl. Acad. Sci.* **1985**, *82*, 5131.
(5) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84.
(6) Holmes, C. P.; Adams, C. L.; Kochersperger, L. M.; Mortensen, R. B.; Aldwin, L. A. *Biopolymers* **1995**, *37*, 199.
(7) Jacobs, J. W.; Fodor, S. P. A. *Trends Biotechnol.* **1994**, *12*, 19.
(8) Carell, T.; Wintner, E. A.; Bashir-Hashemi, A.; Julius Rebek, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2059.
(9) Pirrung, M. C.; CHen, J. *J. Am. Chem. Soc.* **1995**, *117*, 1240.
(10) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419.
(11) Cheng, S.; Comer, D. D.; Williams, J. P.; Meyers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567.

S0002-7863(98)01217-7 CCC: $15.00
Published on Web 08/28/1998

Applications of high-throughput methods in catalysis research have emerged more slowly than in biotechnology and pharmaceutical development.[12] There are several reasons for this, including the following. First, catalysis is a less common event than, for instance, binding of small molecules to a biological target, so the hit rate in completely random screens for catalytic activities is less. Incidentally, it follows that small focused libraries of potential catalysts can be more useful than large random collections of compounds wherein most have few properties suitable for catalytic activities. Second, catalysis in nonbiological systems tends to be hard to detect. High-throughput assays for biological interactions are much better developed than for organometallic systems. Third, impurities tend to have more serious detrimental effects in studies of catalysis, compared with assays to detect simple binding, hence quality control is more important.

Our group is interested in improving the efficiency of asymmetric catalyst discovery and optimization. Evaluation of the arguments presented above led us to conclude that parallel syntheses of catalyst systems coupled with high-throughput automated screens were likely to be the most generally applicable approach.

Generation of the numbers of ligands necessary for screening libraries of catalysts is a challenging problem. We believe that solution-phase syntheses of the required ligands will be the most desirable approach in the majority of situations, for two reasons. First, it is difficult to attain the chemical and optical purities required for reproducible and interpretable studies of asymmetric catalysis via solid-phase syntheses of ligands, particularly for sensitive molecules like phosphines. Second, small focused libraries of catalysts are likely to be more useful than large random libraries, for the reasons discussed above. The number of ligands that must be prepared for focused libraries is manageable, whereas solution-phase synthesis of hundreds or thousands of ligands is impractical. Consequently, solution-phase work has been the focus of our first publications in this area.[12−14] Meanwhile, other groups have concentrated on solid-phase syntheses of ligands as a basis for library development.[15−17] Work is in progress to couple these efforts with split and mix methodologies,[18] and the result is likely to be an extremely elegant demonstration of truly combinatorial syntheses and screens for catalysis.[19] However, the reactions studied in conjunction with solid-phase syntheses of ligands are selected from a limited number of possibilities. This is because nearly[20] all the chiral ligands prepared via solid-phase syntheses so far have been peptidic systems, and the range of catalytic processes that can be mediated with peptide-based ligands is limited.

The task of making a ligand set for screening in small focused libraries is facilitated by a divergent approach.[21] In a divergent ligand synthesis, a large amount of a key optically pure material is produced, then used to prepare many ligands (Figure 2). Members of the ligand set formed may be structurally similar, but that is not problematic because small changes can have relatively large effects on the outcome of asymmetric reactions.

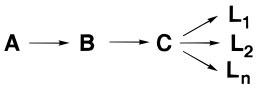


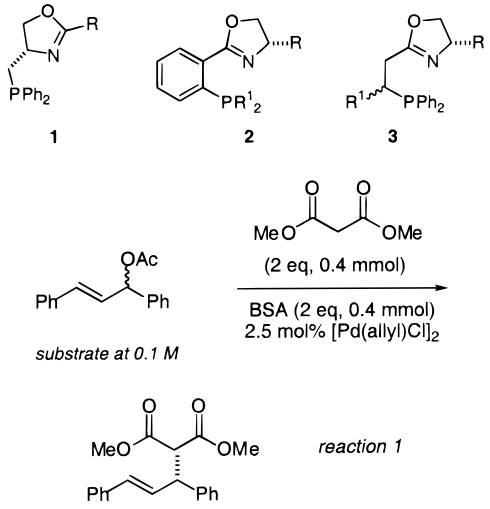
Figure 2. Principle of divergent ligand syntheses.

The concept of divergent ligand syntheses is usually not emphasized, though it frequently emerges as a factor in well-designed approaches to asymmetric catalysts. For instance, Jacobsen's ligands for asymmetric epoxidation[22−26] and other processes[27−33] were developed by combining relatively expensive or less accessible optically active diamines and a variety of readily available salicylaldehyde derivatives. It would be wrong to claim that divergent ligand synthesis is the best strategy for every situation; in fact, it is preferable to obtain ligands directly from commercially available sources, as in the Sharpless epoxidation,[34,35] or in a few synthetic steps, as for bisoxazolines.[36] However, such straightforward access to good molecular architectures for asymmetric coordinating groups is relatively rare. In cases where there is no such convenient strategy, divergent routes to well-designed systems are an attractive option.

This paper highlights divergent, solution-phase syntheses of ligands for generation of focused libraries. It describes how these ligands were used to produce libraries of catalysts in array formats and how data was collected via an automated screen. The novel phosphine oxazoline systems **1** were selected as a test case. High-throughput methods have been used to evaluate and optimize application of these ligands. This study facilitated comparison of ligands **1** with the known systems **2**.[36−42]

(12) Burgess, K.; Porte, A. M. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 2, p 69.
(13) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220.
(14) Burgess, K.; Moye-Sherman, D.; Porte, A. M. In *Molecular Diversity and Combinatorial Chemistry*; Chaiken, I. M., Janda, K. D., Eds.; American Chemical Society: Washington, DC, 1996; p 128.
(15) Gilbertson, S. R.; Wang, X. *Tetrahedron Lett.* **1996**, *36*, 6475.
(16) 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.
(17) 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.
(18) Francis, M. B.; Finney, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 8983.
(19) Jacobsen, E. Conference on Combinatorial Approaches to Chemistry and Biology, Cambridge, U.K., July 1997.
(20) Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712.
(21) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050.
(22) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.
(23) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.
(24) Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.
(25) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457.
(26) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123.
(27) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.
(28) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676.
(29) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.
(30) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889.
(31) O'Connor, K. J.; Wey, S.-J.; Burrows, C. J. *Tetrahedron Lett.* **1992**, *33*, 1001.
(32) Fukuda, T.; Katsuki, T. *SYNLETT* **1995**, 825.
(33) Lam, F.; Xu, J. X.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8414.
(34) Pfenninger, A. *Synthesis* **1986**, 89.
(35) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Taktani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589.
(36) Pfaltz, A. *Acta Chem. Scand.* **1996**, *50*, 189.
(37) Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149.
(38) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769.
(39) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523.
(40) Matt, P. V.; Loiseleur, O.; Koch, G.; Pfaltz, A. *Tetrahedron* **1994**, *5*, 573.
(41) Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595.
(42) Koch, G.; Lloyd-Jones, G. C.; Loiseleur, O.; Pfaltz, A.; Pretot, R.; Schaffner, S.; Schnider, P.; Matt, P. v. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 206.

Ligands **3** are also similar to the new systems **1**; these were prepared by an interesting modular approach, but they have not yet been used extensively.[43] The application chosen for the present study was the allylation of a malonate (reaction 1) so that broader comparisons also could be made with other ligands that have been used in this same transformation.[44]



Despite their similarity, the targeted ligands **1** and systems **2** are different in some critical respects. Ligand **2** is known to form flat six-membered chelates with the chiral center of the oxazoline on one side of the ligand metal plane. Conversely, ligands **1** are expected to form curved five-membered chelates. The R group of ligands **2** is restricted to those found in readily available amino alcohols, whereas we anticipated that the same substituent in ligands **1** could be formed from derivatives of almost any carboxylic acid, giving more scope for diversity. Moreover, the R group in **1** can transmit electronic effects to this ligating center through the C═N bond. In contrast, the R substituents of ligands **2** are electronically insulated from the oxazoline N. At the onset of this work, it was not clear whether ligands **1** would be better than **2** for any particular application in asymmetric catalysis, but it was evident that the two systems would be different.

Results and Discussion

Divergent Synthesis of Phosphine Oxazolines 1. Chiron **6** (Scheme 1) was chosen as a key advanced intermediate for a divergent synthesis of ligands **1**; this material could be prepared in gram quantities from serine. To do this, the BOC-protected ester **4** was prepared from serine via an improvement[45] of earlier procedures.[46,47] Reduction of the ester to an alcohol and tosylation gave the intermediate **5**; no chromatography was necessary and the yield shown is for material obtained after crystallization. Displacement of the tosylate gave a phosphine, which was protected immediately by addition of borane·THF complex. Formation of phosphine borane adducts[48,49] proved to be a useful way to protect phosphorus(III) centers from oxidation throughout this work, and this material has been prepared in 20-g batches. Development of conditions for cleavage of the oxazolidine **6** in good yields required some experimentation. Treatment with 6 M $HCl_{(aq)}$ in ethyl acetate caused rupture of the borane adduct and some oxidation of the liberated phosphine occurred. Tosic acid in methanol at 60 °C gave the desired material, but separation from unwanted byproducts was problematic. However, a solution of anhydrous HCl in methanol at 0 °C gave the corresponding amino alcohol relatively cleanly. The optical purity of a derivative of this material was checked as described in other work from our laboratories.[50]

Several methods to prepare oxazolines from amino alcohols were used in this work.[42,51,52] For instance, ligand **1a** was formed from **7** by reaction with triethyl orthoacetate (method A,[53] Scheme 2). Acylation/cyclization sequences were used for the preparation of some other phosphine oxazolines. Thus, reaction of pivaloyl chloride with **7**, protection of the phosphine as a phosphine borane, mesylation in the presence of DABCO, then slight elevation of temperature gave the *tert*-butyl-substituted ligand **1b** (method B).[51] Use of DABCO in the mesylation step of this sequence increased the pH of the medium and deprotected the phosphine borane in situ.[49] Other ligands were made via reaction of the amino alcohols with imidate esters,[54] e.g. the phenyl-substituted ligand **1i** (method C).[53] Table 1 summarizes the information concerning the synthesis of the library of phosphine oxazolines **1**.

Structure of a Nickel Complex from Phosphine Oxazoline 1i. Complexes of ligands **1** with palladium did not form single crystals suitable for X-ray diffraction. However, ligand **1i** was reacted with nickel bis(tetrafluoroborate) to give the bis-(phosphinooxazoline) complex **8**, and single crystals of this material were formed by slow evaporation of a solution of the complex in dichloromethane/heptane. The ligands adopt a near square planar environment with the two N atoms in a cis orientation relative to each other.

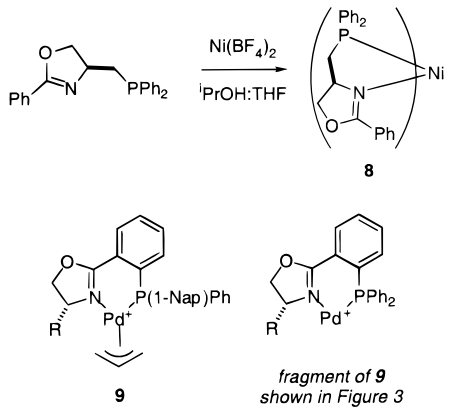
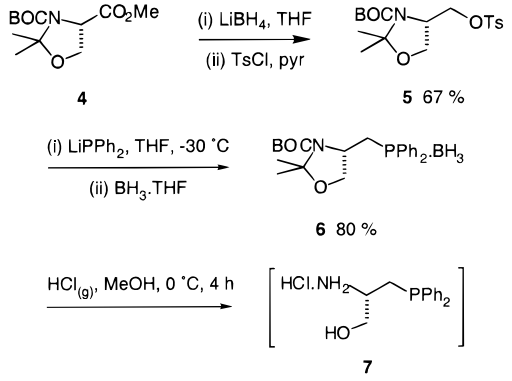


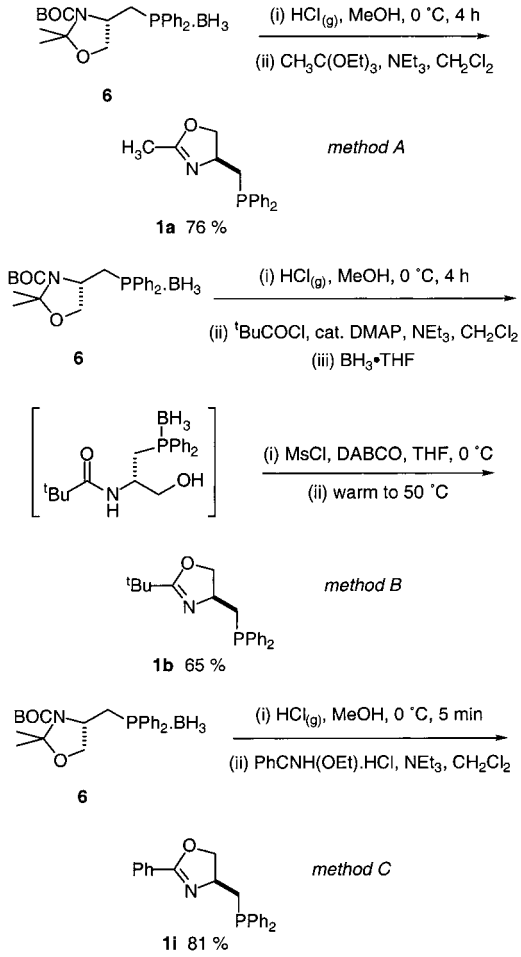
Figure 3 compares a cross section of the nickel complex **8** (generated from crystallographic coordinates obtained in this work) with a similar representation of the palladium complex **9** for which an X-ray structure was obtained by Helmchen and co-workers (coordinates in the Cambridge Crystallographic Database).[39] In complex **9** the alkyl group at the chiral center

(43) Gilbertson, S. R.; Chang, C.-W. T. *Chem. Commun.* **1997**, 975.
(44) Trost, B. M.; Vranken, D. L. V. *Chem. Rev.* **1996**, *96*, 395.
(45) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31.
(46) Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18.
(47) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
(48) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244.
(49) Pellon, P. *Tetrahedron Lett.* **1992**, *33*, 4451.
(50) Porte, A. M.; van der Donk, W. A.; Burgess, K. *J. Org. Chem.* **1998**, submitted.
(51) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884.
(52) Witte, H.; Seeliger, W. *Liebigs Ann. Chem.* **1974**, 966.
(53) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.
(54) Dox, A. W. *Org. Synth.* **1942**, *1*, 5.

Scheme 1



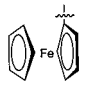
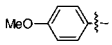
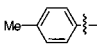
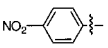
Scheme 2



projects above the plane formed by the N, P, and Pd atoms and to one side of the complex. This group forces the phenyl substituents to adopt an edge−face orientation giving an overall geometry that is conducive to asymmetric induction at the metal. Ligand **1i** in complex **8**, however, is a saucer-shaped ligand. The chiral center in this ligand is centrally placed, and the phenyl-substituent projects out near the metal. It is easy to imagine that this R-substituent might have a greater effect on a η^3-allyl ligand complexed to the metal than on the phenyl groups on the phosphine. That effect, coupled with the curved shape of the ligand, could influence the syn:anti conformational equilibria for the orientation of the allyl group.

High-Throughput Screening. Ligands **1a**−**m** were screened in parallel under various reaction conditions. The simple apparatus shown in Figure 4 was used for this purpose. This

Table 1. Synthesis of the Library of Phosphine Oxazolines **1**

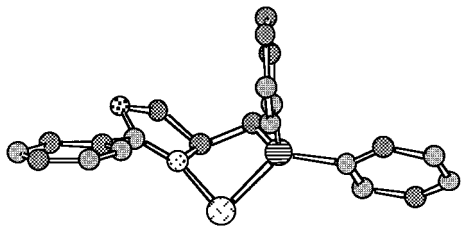
1	R	method	yield (%)
a		A	76
b		B	65
c		B	43
d		B	69
e		B	32
f		B	20
g		B	43
h		B[a]	45
i		C	81
j		C	65
k		C	72
l		C	67
m		B[a]	31

[a] DBU was necessary in method B to induce the cyclization for these compounds; however, it should not otherwise be added because it can bias the reaction toward formation of aziridine byproducts.[51,58]

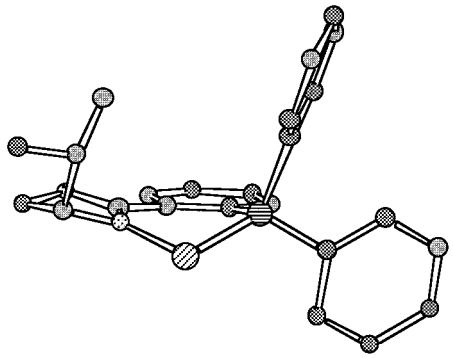
consists of an aluminum block having the same base size as a 96-well microtiter plate, with 34 holes to hold 1.1-mL polypropylene microtubes as reaction vessels. A U-shaped channel was drilled in the block parallel with three sides to facilitate cooling of the block via circulation of cooling fluid from a cryostat. A relatively small hole was drilled in the center of the block to accommodate a thermocouple probe. Another apparatus was also used in some experiments. This was the same except 27 larger wells were used, big enough to accommodate half-dram glass vials. Improved agitation in this case was achieved by adding a small glass bead to each well.

To use the apparatus described above, metal salts and other insoluble solid components of each catalyst system were weighed into appropriate wells. These manipulations were done in a glovebox. Standard solutions of the soluble ligands, reagents, and additives were prepared, and aliquots were pipetted into the wells as appropriate. The reaction vessels were capped then the plate was placed on a commercial (Ika) horizontal shaker for 96-well microtiter plates. For reactions run at reduced temperatures, the block was cooled during mixing of the reaction components, and during the reaction, by circulation of 2-propanol through the U-tube via a cryostat placed outside the box. Placing the thermocouple probe in different wells on the plate demonstrates a uniform temperature to within 1 °C.

The apparatus outlined above was used to set up many reactions in parallel batches. Progress of the reactions was followed via TLC. After the designated reaction time, each reaction mixture was filtered through a silica plug, then analyzed via HPLC using a chiral stationary phase. Use of an automated sampling device was the major time saving aspect of this strategy relative to a sequential approach for which it would not be practical to use an autosampler. The HPLC data also showed the extent of conversion. In every case this was >95% except when silver(1+) ions were added (corresponding to the



8



9

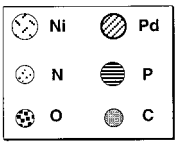


Figure 3. Comparison of solid-state structures of complexes **8** and **9**. Cross sections are shown with part of the naphthyl group of **9** omitted for a better comparison.

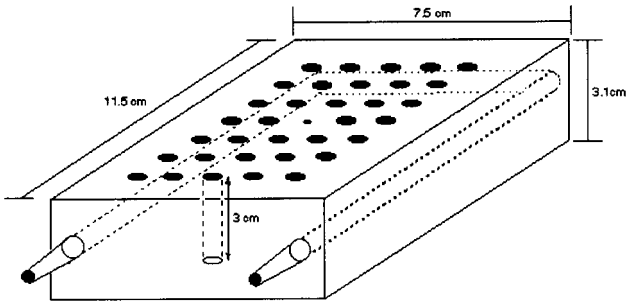


Figure 4. Typical apparatus used to run catalytic reactions in parallel.

enantiomeric excess (ee) data shown in Figure 5c) and when 0.3 M chloride was present (see ee data in Figure 5d).

Two aspects of the high throughput screen outlined above deserve special attention. First, negative results should be interpreted with care since errors in the set-up procedure can occur. Occasionally, data points were repeated because an inexplicable negative result (e.g., no product formation) was originally observed. Similarly, positive results must be checked. This was done by repeating the most important experiments on a larger scale in the conventional way; details of some scale-up experiments are given in the Experimental Section. Second, the strategy saves time, but the normal considerations to reaction scale still apply. Weighing errors will be significant if tiny quantities of the solid materials are used; results are discussed in the section on ligand-to-metal ratio below highlight a situation where this is particularly evident. Consequently, high-throughput screening means ligands and precious metals are consumed faster than in sequential screens, and there is no cheap solution to this problem.

Reproducibility in the screens reported below was gauged in several ways. First, some data points were repeated in separate runs to test plate-to-plate consistency. For instance, the data reported in Figure 5f is from two plates (each data point was recorded once in each, and the average was presented). This was a particularly stringent test of weighing/pipetting errors because, as we shall describe, the ligand-to-metal ratio was an important factor in this work. However, the observed variation was less than ±4% ee in all cases and much less than that for most wells. Similarly, some of the plates had built in controls wherein identical data should have been obtained for selected data points in two different experiments, and good correspondence was obtained. Checks of the overall reliability of the data collected in plates emerged when key reactions were scaled-up, and the correspondence was high (see the Experimental Section for some comparisons). However, we do not claim that reproducibility will be high for every type of catalytic transformation that researchers may wish to test in this type of plate reactor. Research not described in this manuscript has indicated that reproducibility can be problematic when a key reagent is insoluble in the reaction medium or when two immiscible solvents form a biphase system.

In this work, parallel syntheses and automated screens facilitated rapid accumulation of large amounts of data on the application of ligands **1** in the allylation reaction 1. Details of that data are discussed in the following subsections.

Solvent Effects. Enantiomeric excesses were measured for identical reactions but using three solvents and seven different ligands (Figure 5a). Overall, the solvent effects were not striking, probably of a magnitude near the experimental error for the system. Nevertheless, it appears that the best solvent is usually dichloromethane because catalysts in this solvent gave the highest selectivities for four of the seven ligands investigated in this phase of the work.

Electronic Effects of the Ligand R-Substituent. Comparison of the enantioselectivities observed for the different R-substituents (Figure 5a) indicates that aryl rings with electron releasing para substituents (Me or OMe) tend to give higher enantioselectivities than similar groups with electron-withdrawing substituents (4-NO_2 and C_6F_5). Enantioselectivities for the 4-methoxybenzene R-group (ligand **1j**) were highest for the ligands shown in Figure 5a (up to 82% ee), and those for the pentafluorophenyl R-substituent were the worst. Curiously, a trifluoromethyl substituent (ligand **1h**) gave a stereoselectivity that was small and reversed relative to all the other ligands, including the methyl-substituted one. Overall, it seems that high enantiodiscriminations seem to be facilitated by electron-rich oxazoline substituents, though the effect is not large. Finally, these conclusions must be qualified because steric factors must be operative in this series. This is true even within the series of aryl-substituted oxazolines because their para substituents projected into a region of space alongside the metal and not too far from the allyl ligand in the putative intermediates.

Steric Effects of the Ligand R-Substituent. Figure 5b correlates enantioselectivities with ligands of different sizes by similar electronic demands. Substituent size/shape issues have more significant effects than the electronic features discussed above. Highest enantiodiscrimination in this work was observed for the adamantyl ligand **1e** (94% ee). Some ligands with smaller or larger R-substituents gave much lower enantioselectivities; for instance, the methyl ligand **1a** gave a product of only 53% ee and for the triphenylmethyl system **1d** the ee was reversed to −6%. Exactly why the pseudo-spherical shape of the adamantyl substituent is preferable to the others is a matter

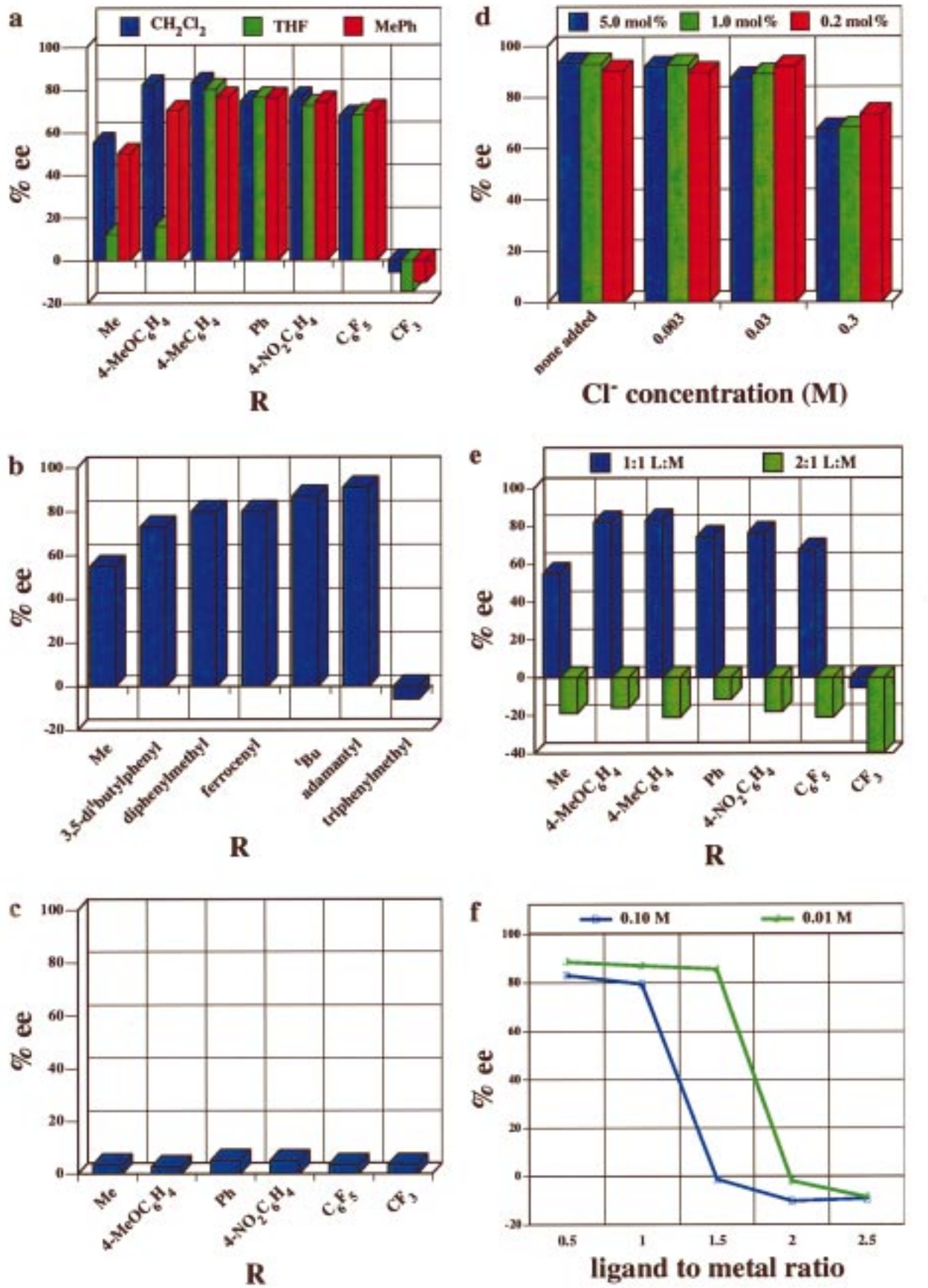
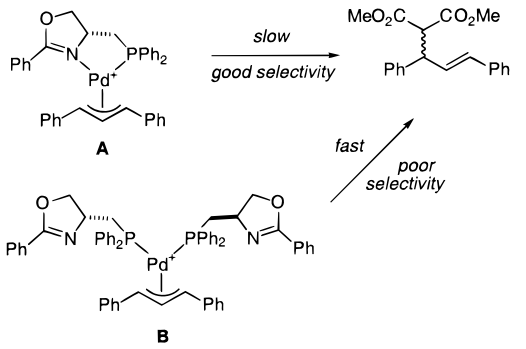


Figure 5. Correlations of enantioselectivities with (a) solvent and ligands selected for variable electronic effects, (b) ligands selected for steric variability, (c**)** ligands in the presence of a chloride abstracting agent, (d) ligands and three concentrations of added *n*-Hex_4NCl, (e) ligands and ligand-to-metal ratio, and (f) ligand **1i** with various ligand-to-metal ratios at two different catalysts concentrations. Unless otherwise stated, the solvent was CH_2Cl_2 throughout, and the conditions were as specified in reaction 1. Throughout, positive enantioselectivities indicate that the *S*-enantiomer of the allylation product was formed in excess.

Scheme 3



for speculation. However, these data illustrate an observation that may be general: substituent bulk is less important than the specific regions of space that are occupied, i.e. substituent topography can be more relevant than size in asymmetric processes.

Effects of Chloride. Detrimental effects can be very conspicuous in screens of the type outlined above. Figure 5c shows data collected from the first library in which $AgPF_6$ was added to remove chloride from the system. Less than 8% enantiomeric excess was observed for each of the six ligands tested, whereas much higher selectivities were seen in most of the other reactions run in parallel.

Having established the negative effects of abstracting chloride from the system, experiments were performed to access the consequences of adding chloride. These studies seemed particularly appropriate because others have noted advantages of adding halides to asymmetric allylation reactions.[43,55] Figure 5d shows data from experiments in which enantiomeric excesses were monitored as a function of two variables: amount of tetra-*n*-hexylammonium chloride added and different mole percentages of catalyst. The two lower concentrations of added chloride had small effects that diminished or enhanced the enantioselectivity, apparently depending on the mol % catalyst used. However, addition of 0.3 M chloride consistently reduced the enantioselectivity of the reaction. The rate of the reaction was also decreased such that conversions on the order of 80% were obtained in the indicated reaction time.

Effects of Ligand-to-Metal Ratio. Variations of ligand-to-metal ratio had the most profound effects observed in this work (Figure 5e). Figure 5f shows that when the ligand-to-metal ratio was increased above approximately 1:1 the enantioselectivity falls precipitously. That plot also demonstrates that the absolute concentration of the catalyst (as opposed to the ratio of the ligand:metal) has an affect, though not such a dramatic one. When the catalyst is at lower concentrations (0.01 M as opposed to 0.1 M), the sharp drop in enantioselectivity as a function of ligand-to-metal ratio occurs at above 1.5:1.0. Each point in Figure 5f is the average of two values obtained from two plate experiments set up and run on different occasions; good agreement between the two sets of experiments was observed, demonstrating the reproducibility of these observations and the screening technique in general.

An explanation for the pronounced effect of ligand-to-metal ratio is outlined in Scheme 3, supported by the following rationale. The chelated π-allyl intermediate **A** predominates at ligand-to-metal ratios of less than 1:1. Attack of malonate on **A** takes place at the allyl carbon trans to the phosphorus atom[56] because phosphorus is a better π-acceptor than nitrogen, making that carbon relatively electron deficient. For that same reason, complexes with two phosphines coordinated to palladium will tend to react faster than those with one P- and one N-ligating group. At higher ligand-to-metal ratios than 1:1, complex **B** is formed in appreciable amounts. This intermediate reacts faster than **A** because it has two ligating phosphines. It also reacts with less enantiodiscrimination than **A** because it has more degrees of freedom. Low concentrations of catalyst disfavor formation of complex **B**; consequently, enantioselectivities do not diminish until a higher ligand-to-metal ratio is reached.

The explanation presented above is not the only possibility, but it fits the data better than the alternatives we could envisage. For instance, it is conceivable that the effects of ligand-to-metal ratio were due to formation of catalytically active di- or polynuclear complexes. However, to invoke this explanation would suggest that these di- or polynuclear catalysts give enantioselectivities superior to those of the monometallic systems because their formation would be disfavored at high ligand-to-metal ratios. We think this is less likely than the explanation outlined in Scheme 3.

The following experiments were performed to probe the composition of the catalyst mixtures at various ligand-to-metal ratios. The complex $[(\eta^3\text{-allyl})PdCl]_2$[57] mixed with ligand **1k** in $CDCl_3$ in a ratio of 1:1 gave a ^{31}P NMR spectrum with one major peak at 17 ppm. Similarly ligand **2** (R = Ph) mixed in a 1:1 ratio with $[(\eta^3\text{-allyl})PdCl]_2$ gave a ^{31}P NMR spectrum with a major peak at 20 ppm, implying that a similar complex was formed. Another 0.5 equiv of the appropriate ligand was then added to each mixture, and their NMR spectra were recorded again. The ^{31}P NMR spectrum of the mixture containing **2** showed a new peak at −10 ppm corresponding to the uncoordinated phosphine, as well as the original peak at 20 ppm. However, in the experiment with **1k**, no free phosphine was observed; instead, the peak at 17.4 disappeared, leaving a very broad peak around 15 ppm at 20 °C. Upon cooling the solution to −60 °C the peaks sharpened, showing two inequivalent phosphines at 14 and 11 ppm coupled to each other.[56] These results show that excess ligand **1k** induces the complexes involved to undergo a type of dynamic behavior that is not observed for the Helmchen−Pfaltz−Williams ligand **2**.

Conclusions

Asymmetric catalysis, especially for systems prepared in situ or using additives, is mechanistically complex. Researchers attempting to discover and optimize catalytic systems may be aware of the degree of complexity, but they are often forced to assume that all of the variables are independent because they do not have the capacity to proceed any other way. Consequently, a typical experimental approach is to hold all but one parameter constant, find the optimal condition for this variable and retain it, then proceed to the next variable. However, *critical parameters for catalysis are often mutually dependent*. For instance, Figure 5a indicates that the best enantioselectivity was obtained for the 4-methoxybenzene-substituted ligand when dichloromethane was used as a solvent. Dichloromethane is not the best solvent for all catalytic systems for this transformation though, even within this set of similar ligands. Toluene and THF were better solvents for the stereoselective allylation when the pentafluorophenyl ligand was used. This type of correlation only becomes apparent in a two-dimensional screen

(55) Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron* **1997**, *8*, 155.
(56) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2108.
(57) Matt, P. v.; Lolyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Ruegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265284.
(58) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *35*, 907.

wherein enantiomeric excess is monitored as a function of the solvent and ligand substituent.

Solutions to multidimensional problems in discovery and optimization of catalysts, particularly asymmetric catalysis, require high-throughput screens. Design and chemical intuition are only valuable for setting boundary conditions. For example, the notion that ligands of structure **1** are likely to be useful in asymmetric allylation reactions is a useful guiding principle, but it provides no insight into details which may be critical for good catalysis. In fact, it is impossible to reliably select a complete set of ideal experimental parameters using design and chemical intuition alone, especially if some show high degrees of mutual variability. Therefore, we suggest that high-throughput syntheses and screening techniques have enormous, and largely unexplored, potential in catalyst development.

At the end of this study, despite the many experiments that were performed on ligands **1**, the highest enantioselectivities obtained (i.e., with ligand **1e**) are approximately 5% less than the best that have been obtained in this allylation reaction. In retrospect, we attribute this to a minor flaw in the design of ligands **1** rather than to lack of effort in the optimization process. The five-membered chelate formed when these ligands complex may be relatively strained and inclined to open, giving complexes such as **B** in Scheme 3 that then react with poor enantiodiscrimination. That assertion is supported by the ^{31}P NMR studies described above. If this hypothesis is correct, the degree of asymmetric induction could be enhanced in a less strained chelate that would be less prone to dynamic behavior. Significantly, ligands **2** and **3**, which can form six-membered ring chelates, give marginally better enantioselectivities than our best ligand in the allylation reaction 1, perhaps for this reason. Further studies on a second generation of phosphine oxazolines having the potential to form larger ring chelates are in progress.

Experimental Section

General Procedure for Screening of Catalyst Systems in a 34-Well Plate. In a dinitrogen atmosphere, allylpalladium chloride dimer (0.36 mg, 0.001 mmol) was weighed into the microtube reaction vessel. A 0.004 M stock solution of the ligands was prepared, appropriate amounts were added to each well as required via a pipet-man, and the solutions were diluted to a total volume of 200 μL by adding additional solvent. The solutions were then cooled to 0 °C in the block apparatus. After 0.5 h of equilibration time, a 0.2 M stock solution of 1,3-diphenylpropenyl acetate (200 μL, 0.04 mmol) was added to each well using a pipet-man, followed by neat dimethyl malonate (10 μL, 0.08 mmol), *O,N*-bis(trimethylsilyl)acetamide (20 μL, 0.08 mmol), and solid potassium acetate (0.5 mg, 0.005 mmol). The block was agitated for 12 h on a horizontal shaker designed for 96-well microtiter plates. The block was removed from the inert atmosphere, and the contents of each well were concentrated to dryness on speed vacuum apparatus, dissolved in 60:40 hexanes/EtOAc, and then manually passed through a short silica plug (60:40 hexanes/EtOAc). The reaction mixture was analyzed via HPLC (Chiralcel OD analytical column; eluting with 99:1 hexanes/2-propanol, flow rate 0.5 mL/min, 254 nm, t_1 = 20.5 min for *S*-enantiomer, t_2 = 21.4 min for *R*-enantiomer). The HPLC separation was calibrated using racemic material.

Representative Procedure for Larger Scale Reactions. Allylpalladium chloride dimer (0.90 mg, 0.005 mmol) and the ligand (**1e** in this case, 0.009 mmol) were weighed into half-dram vials, each equipped with a small glass bead to enhance agitation, under a dinitrogen atmosphere. The vials were placed into the 27-well reaction block. Dichloromethane (800 μL) was micropipetted into each vial, and the solutions were cooled to 0 °C and allowed to equilibrate for 0.5 h. A 0.2 M stock solution of 1,3-diphenylpropenyl acetate (1 mL, 0.20 mmol) was added, followed by neat dimethyl malonate (46 μL, 0.40 mmol), *O,N*-bis(trimethylsilyl)acetamide (100 μL, 0.4 mmol), and solid potassium acetate (2 mg, 0.02 mmol). The reaction block was agitated for 12 h on a horizontal shaker designed for 96-well microtiter plates, then removed from glovebox. The solvent was removed, and the residue was purified via flash chromatography (90/10 hexanes/EtOAc) to give 50.6 mg of product (78%). The optical rotations of product were compared with the literature rotation[38] to assign absolute configurations.

Other larger scale rections, performed exactly as denoted above but with other ligands, gave the following data (ligand, % ee, % yield): **1a**, 55% ee, 94%; **1i**, 86% ee, 79%; **1e**, 90% ee, 78%. These ee data compare well with those obtained from the high-throughput screens, establishing the reproducibility of the screening procedures.

Acknowledgment. We thank Dr Wilfred van der Donk (University of Illinois, Urbana) for valuable discussions. Support for this work was provided by The Petroleum Research Fund, administered by The American Chemical Society, and by The Robert A. Welch Foundation. K.B. thanks the NIH Research Career Development Award and The Alfred P. Sloan Foundation for a fellowship. We also thank scientists at Johnson-Matthey for helpful discussions and support.

Supporting Information Available: Experimental procedures and characterization details for the phosphine oxazolines and data for the crystallographic analysis of compound **8** (35 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981217K