Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries

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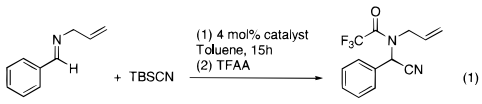
Combinatorial chemistry is now well-recognized as a promising strategy for the discovery and optimization of ligands for biological targets, and it has more recently emerged as a viable approach toward the identification of novel catalysts,[1] coordination complexes,[2] and solid-state materials.[3] Two fundamentally different strategies—split-and-pool and parallel library synthesis—can be distinguished within combinatorial chemistry, and the choice of method depends on the problem at hand.[4] The split-and-pool strategy may be advantageous when it is desirable or even necessary to evaluate large numbers of compounds because little is known about the target structure and the proportion of compounds with the sought-after activity is likely to be extremely low.[5] The parallel library approach can be most viable for lead optimization, where the basic features of the target structure have already been established.[6] In this case, the greater experimental simplicity associated with screening and identifying spatially arrayed candidate structures can override the possible advantages associated with evaluating larger libraries. We have explored this latter scenario in the context of asymmetric catalysis, with the synthesis of parallel combinatorial libraries of a known class of chiral ligands,[7] and their evaluation as catalysts for the asymmetric hydrocyanation of imines (the Strecker reaction) (eq 1). In this paper, the viability of the approach is illustrated by the iterative optimization of reaction enantioselectivity from an initial lead result of 19% ee to 91% ee through a sequence of nonobvious modifications in the catalyst structure.



(1)

The initial step in the implementation of the parallel catalyst library strategy was the selection of a potential catalyst system that was amenable to solid-phase synthesis and systematic structural variation and also known to be a selective template for chirality transfer. These stipulations dictate high-yielding and generalizable synthetic access to the catalyst with an unobtrusive site for attachment to the solid support. Unfortunately, these criteria are not all met in most of the best known and most effective chiral ligand systems, such as binaphthyl-based ligands, C_2 symmetric phosphines, salen ligands, bisoxazolines, and tartrate- and cinchona alkaloid-derived compounds. In contrast, tridentate Schiff base complexes constitute an emerging class of catalysts[8] that might be amenable to solid phase synthesis. These systems are typically comprised of three units, a chiral amino alcohol, a salicylaldehyde derivative, and a metal. We chose to modify the core structure such that the amino alcohol was replaced with a diamine, with the second nitrogen on the chiral backbone serving as the site for attachment to the solid support (Figure 1). An amino acid was incorporated as an additional diversity element between the diamine and the polymer support. The resulting ligand system was evaluated and optimized for the reaction in eq 1 by carrying out the transformations in parallel with the polymer supported catalysts in individual reaction vessels[9] and assaying the product mixtures with a commercial autosampler by chiral GC analysis.

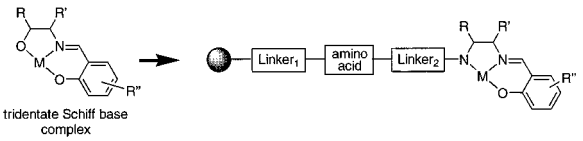


Figure 1. Concept for the solid-phase synthesis of tridentate Schiff base complexes.

Library 1. One ligand of the type in Figure 1 was prepared and evaluated for catalysis of addition of TBSCN to *N*-allylbenzaldimine in the presence of a series of different metal ions. Whereas comparable reactivity was observed in each case, ligand in the absence of any added metal ion proved to be the most enantioselective (19% ee). This result was not entirely unexpected given the fact that the only reported example to date of an enantioselective Strecker catalyst is a nonmetal containing cyclic dipeptide.[10]

Library 2. Based upon this initial lead result, a parallel ligand library of 48 members was prepared and screened in the absence of any added metal ions.[11] The amino acid component was observed to exert a very significant effect on reaction enantioselectivity, with leucine-derived catalysts providing the best results. The relative stereochemistry of the catalyst was also important, with (*R*,*R*)-diamine-derived catalysts affording substantially higher ee's when coupled with L-leucine than with the unnatural D-leucine enantiomer (e.g., Leu-CH-D: 32% ee; D-Leu-CH-D:

(1) For reviews and discussions, see: (a) Gennari, C.; Nestler, H. P.; Piarulli, U.; Salom, B *Liebigs Ann./Recueil* **1997**, 637. (b) Borman, S. *Chem. Eng. News* **1996**, *74*, 4(45), 37.

(2) (a) Francis, M. B.; Finney, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 8983. (b) Burger, M. T.; Still, W. C. *J. Org. Chem.* **1995**, *60*, 7382. (c) Malin, R.; Steinbrecher, R.; Jannsen, J.; Semmler, W.; Noll, B.; Johannsen, B.; Frömmel, C.; Höhne, W.; Schneider-Mergener, J. *J. Am. Chem. Soc.* **1995**, *117*, 11821. (d) Hall, D. G.; Schultz, P. G. *Tetrahedron Lett.* **1997**, *38*, 7825. (e) Shibata, N.; Baldwin, J. E.; Wood, M. E. *Biorr. Med. Chem. Lett.* **1997**, *7*, 413.

(3) (a) Briceño, G.; Chang, H.; sun, X.; Schultz, P. G.; Xiang, X.-D. *Science* **1995**, *270*, 273. (b) Danielson, E.; Golden, J. H.; McFarland, E. W.; Reaves, C. M.; Weinberg, W. H.; Wu, X. D. *Nature* **1997**, *389*, 944. (c) Brocchini, S.; James, K.; Tangpasuthadol, V.; Kohn, J. *J. Am. Chem. Soc.* **1997**, *119*, 4553. (d) Baker, B. E.; Kline, N. J.; Teado, P. J.; Natan, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 8721.

(4) For recent reviews on strategies for the synthesis and evaluation of small-molecule libraries, see: (a) Hobbs DeWitt, S.; Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 114. (b) Thomson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (c) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (d) Still, W. C. *Acc. Chem. Res.* **1996**, *29*, 155. (e) Terret, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135.

(5) See, for example: (a) Combs, A. P.; Kapoor, T. M.; Feng, S.; Chen, J. K.; Daudé-Snow, L. F.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 287. (b) Cheng, Y.; Suenaga, T.; Still, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 1813. (c) Liang, R.; Yan, L.; Loebach, J.; Ge, M.; Uozumi, Y.; Sekanina, K.; Horan, N.; Gildersleeve, J.; Thompson, C.; Smith, A.; Biswas, K.; Still, W. C.; Kahne, D. *Science* **1996**, *274*, 1520.

(6) See, for example: Kick, E. K.; Roe, D. C.; Skillman, A. G.; Liu, G.; Ewing, T. J. A.; Sun, Y.; Kuntz, I. D.; Ellman, J. A. *Chem. Biol.* **1997**, *4*, 297.

(7) For related efforts, see: (a) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220. (b) Cole, M. B.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668.

(8) (a) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1975**, 1707. (b) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385. (c) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (d) Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2641.

(9) Reactions were carried out in 1 mL glass test tubes. Details are provided in the Supporting Information.

(10) (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (b) In independent investigations, we have recently identified Al-based asymmetric catalysts for the Strecker reaction: Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.*, in press.

(11) Enantioselectivity data for Library 2 are provided in the Supporting Information.

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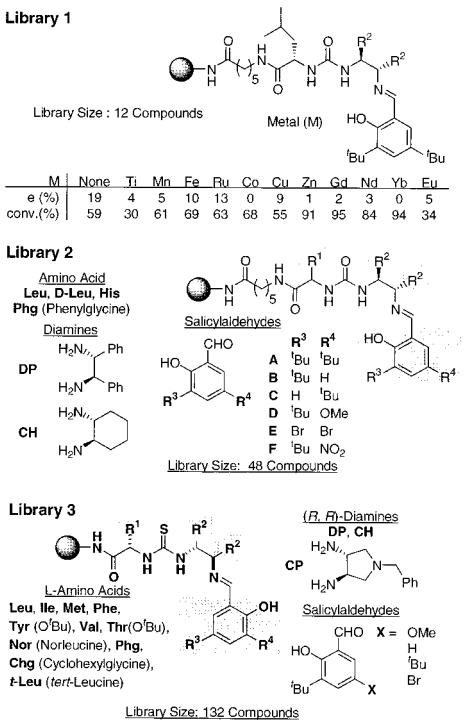
Chart 1



5% ee). Finally, the substituents on the salicylaldehyde derivatives were also found to play a critical role, with 3-*tert*-butyl substituted derivatives A, B, and D affording highest ee's.

At this stage of the development of the catalyst libraries, the linker elements (Figure 1) were optimized by a classical, one-catalyst-at-a-time, approach. Control experiments revealed that the caproic acid unit used to link the catalyst to the resin in Libraries 1 and 2 ($Linker_1$) was responsible for a nonnegligible level of background reactivity. Direct attachment of the amino acid group of the catalyst to the polystyrene support resulted in improved enantioselectivity for the best catalysts indentified from Library 2 (e.g., 30−45% ee with Leu-CH-A). The unit used to link the amino acid to the diamine ($Linker_2$) was also found to influence catalyst enantioselectivity. For example, in the Leu-CH-A series, replacement of the urea linker with thiourea led to an enhancement in ee from 45% to 55%, whereas the corresponding guanidine-linked system effected the same Strecker reaction with only 21% ee.

Library 3. On the basis of the results obtained from Library 2, a larger parallel library of 132 thiourea derivatives was prepared incorporating only nonpolar L-amino acids and 3-*tert*-butyl substituted salicylaldehyde derivatives. All library members were found to catalyze the reaction in eq 1, with *t*-Leu-CH−OMe (OMe denoting 3-*tert*-butyl-5-methoxysalicylaldehyde, D in Library 2) affording the highest enantioselectivity (80% ee, Figure 2). The amino acid component was again seen to be crucial, with the bulkiest derivatives (*t*-Leu, cyclohexylglycine, and isoleucine) providing best results. Interestingly, *t*-Leu proved to be the best amino acid component for CH-derived catalysts, but the worst one for CP derivatives, effectively highlighting the benefit of evaluating all ligand permutations.

The best catalyst identified from the library screens, *t*-Leu-CH−OMe, was synthesized independently in solution and tested in the asymmetric reaction in eq 2. With HCN as the cyanide source, the solution-phase catalyst **1** catalyzed the formation of the Strecker adduct of *N*-allylbenzaldimine in 78% isolated yield and 91% ee at −78 °C. Even though **1** was optimized for that particular substrate, it proved to be an effective catalyst for a range of imine derivatives, affording product with moderate-to-high enantioselectivity and yield (Table 1). It is especially

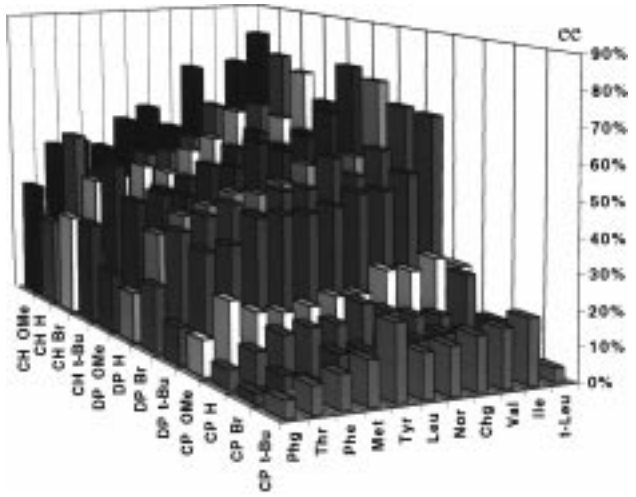


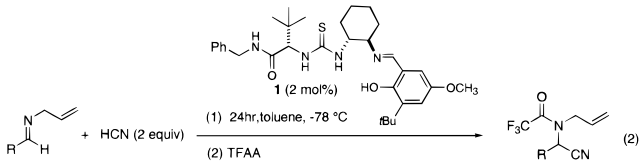
Figure 2. Enantioselectivities obtained with Library 3.

Table 1

entry	R	yield[a] (%)	ee[b] (%)
a	Ph	78	91
b	*p*-$OCH_3C_6H_4$	92	70
c	*p*-BrC_6H_4	65	86
d	2-napthyl	88	88
e	*tert*-butyl	70	85
f	cyclohexyl	77	83

[a] Isolated yield. [b] All ee's were determined by GC or HPLC chromatography using commercial chiral columns. See Supporting Information.

noteworthy that aliphatic imine derivatives (entries e−f) underwent hydrocyanation with >80% ee. This constitutes the first example of high enantioselectivity in the Strecker reaction with this important class of substrates.[10]



This study demonstrates that chiral Schiff bases identified from parallel synthetic libraries can be effective asymmetric catalysts for the Strecker reaction. These systems not only exhibit promising enantioselectivity both on solid phase and in solution but are also easily prepared from inexpensive components. The structural features that lead to high enantioselectivity are quite unanticipated, with nonintuitive synergystic effects displayed between catalyst components. These results raise interesting questions concerning the mechanism of catalysis of the hydrocyanation reaction. Experiments are in progress to address this issue, to further develop this new class of catalysts for the Strecker reaction, and finally to identify effective asymmetric catalysts for other important reactions using this parallel approach.

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Supporting Information Available: Experimental details on library and metal complex preparation and reaction screening; characterization of solution phase catalyst **1**; enantioselectivity data for Library 2; and ee analyses of products from Table 1 (15 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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