Investigation of a New Family of Chiral Ligands for Enantioselective Catalysis via Parallel Synthesis and High-Throughput Screening

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Applications of combinatorial chemistry are widespread and cover fields as diverse as drug discovery and optimization,† material science,‡ studies of molecular recognition,§ and the development of new catalysts.†,‡,§ In particular, the possibility of high-throughput catalyst screening for the development and optimization of enantioselective reactions has generated a lot of excitement.†,‡,§ Two different basic approaches have been considered: optimization of the reaction conditions (solvents, temperatures, stoichiometries, different ligands, or metal ions)§ and the synthesis of new ligands.§,† The synthesis of new ligands via a modular building block strategy in which the stereochemical properties of a metal binding site (e.g., a diphosphine§ or a Schiff-base§) and the stereoelectronic properties of a metal binding site (e.g., a diphosphine§ or a Schiff-base§) are tuned by variation of the substituents and side chains. In the case of screening members of a library containing ligands for enantioselective catalysis, the identification of a hit requires a demanding selection procedure, since the screen is ultimately catalyzing a reaction and analysis of its stereochemical outcome. For this reason, a combinatorial system is usually chosen that allows the synthesis of discrete isolated compounds. Parallel synthesis (as opposed to the “split and pool” methodology)§ allows one to know the identity of each ligand and keeps the ligands separate so that screening of individual ligand metal complexes can be performed.

We have developed a new family of chiral ligands based on a modular building block strategy and on the use of a disulfonamide as metal chelating unit, for which a number of examples are already known.§ These ligands are synthesized by coupling commercially available vicinal diamines 1 and a novel class of chiral N-protected D-amino sulfonyl chlorides of general formula 2 (Scheme 1), obtained in high yields from L-α-amino acids via a straightforward synthetic protocol.§ For the construction of the library (30 compounds), we used the sulfonyl chlorides derived from L-alanine (2g), L-valine (2h), L-leucine (2i), l-phenylalanine (2j), and L-proline (2k).§,† As for the diamine part of the library, we employed two vicinal diamine scaffolds: 1,2-diaminocyclohexane§ (1a–d) and 1,2-diphenylethylenediamine§ (1e–f), for which effective use in the fields of asymmetric synthesis and molecular recognition is well documented. In the case of 1,2-diaminocyclohexane, besides the chiral trans-R and trans-S,§ we have used the achiral cis-R,S and the racemic (±) trans structures to take into consideration all the possible stereochemical combinations, including those that may seem odd at first glance, and to take advantage of possible cooperative effects arising from the formation of aggregates.†,‡,§

In principle, the synthesis and subsequent test of the library could be accomplished with the ligands bound to a solid support. However, the need for an additional handle to attach the diamine scaffold to the support and the controversial role of the solid matrix on the yield and enantiomeric ratios (er’s) of the catalyzed reactions†,‡,§,12 make this route less attractive. On the other hand, the classical synthesis in solution suffers from a major disadvantage, i.e., the necessity of workup and purification (chromatography), which makes parallel chemistry impractical. An answer to these problems was found with the use of solid-phase extraction (SPE) techniques.†,‡ For the coupling reactions (Scheme 1), we treated the vicinal diamines 1 with an excess of sulfonyl chlorides 2 to ensure complete conversion and

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In the case of proline, problems with the preparation of the N-Boc-protected sulfonyl chlorides via the usual route suggested the alternative use of N-Boc-protected sulfonyl chlorides.
used SPE methodology to avoid purification of the sulfonamide products 3. The reaction was run in DCM in the presence of polymer bound “dimethylamino pyridine”\(^\text{13}\) to catalyze the coupling reaction and scavenge the liberated HCl; after all the diamine had been converted into the disulfonamide, the excess of sulfonyl chloride was removed by reaction with solid-phase bound tris(2-disulfonamide derivative, the excess of sulfonyl chloride was then purified (chromatography) and fully characterized, and the screening results were confirmed by reaction with the four separate aldehydes on a preparative scale (1 mmol). (2) The influence of the different \(\beta\)-aminosulfonfyl side chains in controlling the er’s is as follows: R\(^1\) = CH\(_3\)Ph \((2j) \> \) CH\(_3\) \((2g) \> \) i-Bu \((2i) \> \) i-Pr \((2h) \> \) (CH\(_2\))\(_3\) \((2k)\). (3) The influence of the different scaffolds in controlling the er’s is as follows: trans-(15,25)-diaminocyclohexane \((1b) \> \) cis-diaminocyclohexane \((1c) \approx \) (E)-1,2-diaminocyclohexane \((1d) \> \) (1R,2R)-diphenylethylenediamine \((1e) \approx \) (15,25)-diphenylethylenediamine \((1f) \> \) trans-(1R,2R)-diaminocyclohexane \((1a)\). (4) With the cis and the racemic scaffolds, moderate enantioselectivities were obtained in favor of the (R)-alcohol \([3ci, R:S = 87:13 (5m), 88:12 (5o), 3dj, R:S = 80:20 (5m), 81:19 (5n); 3di, R:S = 80:20 (5o)]\). (5) With the (R,R)-diphenylethylenediamine scaffold, one single reasonably high enantiomeric ratio was obtained \([3ej, R:S = 89:11 (5o)]\).

The use of the chiral ligand library \((3ag-3fk)\) in other enantioselective reactions of synthetic importance is presently under investigation.

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Supporting Information Available: Experimental procedures for the library synthesis (30 compounds 3ag–3fk) and screening and additional experimental procedures including physical and spectroscopic data for compounds 2g–2k, 3bj, and 5l–5o (8 pages).

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