ELSEVIER

Journal of Organometallic Chemistry 567 (1998) 3–6

Journal of Organometallic Chemistry

New screening methodologies or combinatorial chemistry applied to asymmetric catalysts

Henri B. Kagan *

Institut de Chimie Moléculaire d'Orsay and Institut Universitaire de France, Université Paris-Sud, 91405 Orsay, France

Received 8 December 1997

Abstract

Fast optimization of a chiral catalyst and chiral ligands prepared by combinatorial chemistry are reviewed. The case of a one-pot multi-substrate screening of a chiral catalyst has been also discussed. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Asymmetric catalysis; Combinatorial chemistry; Chiral ligand; Fast screening

1. Introduction

Within less than one decade the combinatorial chemistry establishes itself as an attractive approach to prepare libraries of compounds able to be tested for their biological activities [1–3]. The biological tests may be carried out either in solution or more conveniently on mixture of beads carrying the compounds. The extrapolation of this approach to the research of new chiral catalysts gives some problems which will be discussed in the following section. Then the main reports on syntheses of chiral catalysts by combinatorial methods will be reviewed as well as the screening of new ligands.

2. Problems specific to asymmetric catalysis

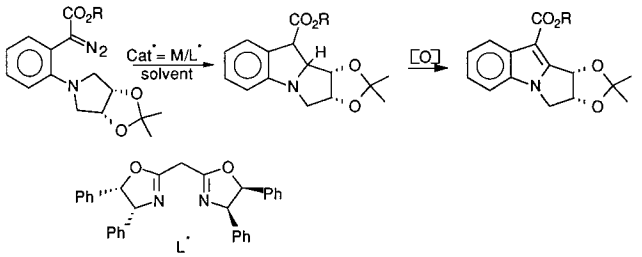
It is often necessary to tune the structure of a chiral catalyst in order to optimize its enantioselectivity in the transformation of a given substrate. A nice example is the Sharpless dihydroxylation where a large family of alkaloid derivatives allows to solve almost all the problems [4].

If a chiral ligand of a catalyst is prepared from several building blocs one may apply the method of combinatorial chemistry and generate a myriad of different ligands. Some examples will be shortly mentioned in the next paragraph. The problem comes with the fast evaluation of the large number of new chiral catalysts which have been obtained. The screening of the mixture of the catalysts in solution is impracticable, because of the confusion arising from the formation of (*R*) and (*S*) products by competitive pathways. It may be well that two catalysts could give high ee but products of opposite absolute configuration, the overall result being a racemic mixture. In order to overcome this handicap specific to asymmetric synthesis it is necessary to perform a parallel screening where each catalyst is individually studied (vide infra).

However the evaluation of one given catalyst versus a set of different substrates is also quite informative, we have developed this approach (see below). In that case each substrate generates a pair of enantiomers, the problem is to fixed a method able to analyze the ee's of the various products.

* Fax: +33 1 69154680.

PII S0022-328X(98)00660-3



Scheme 1. Ninety-six parallel screenings for catalyzed carbene C–H insertion, with variation on M ($AgSF_3$, $La(OTf)_3$, $RhNBD^+$, CuOTf, etc.) and solvent (THF, CH_3CN, $CHCl_3$ or toluene)) (from ref. [5]).

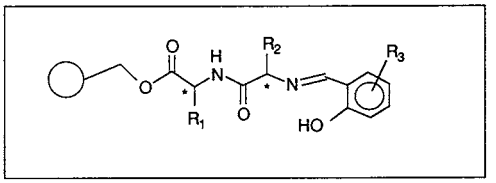
3. Fast optimization of a chiral catalyst

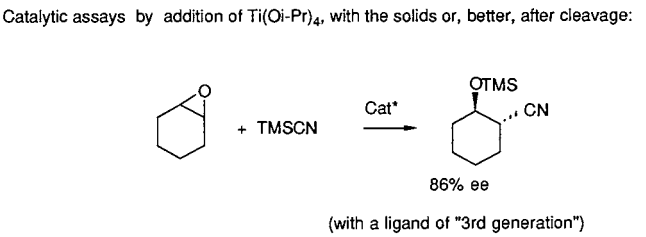
Burgess et al. [5] described the use of a plate with 96 wells for optimizing an asymmetric carbene C–H insertion. For example a chiral ligand was studied in various conditions, by using four different solvents and 7 metal complexes (Scheme 1). By this way a new silver catalyst has been discovered for the above reaction.

4. Synthesis of chiral ligands by combinatorial methods

Various authors applied methods of combinatorial chemistry to prepare libraries of chiral ligands. The ligands were synthetized on beads, in several steps.

Ellman et al. [6] prepared a large number of amino alcohols starting from (*S*)-hydroxyproline (Scheme 2).

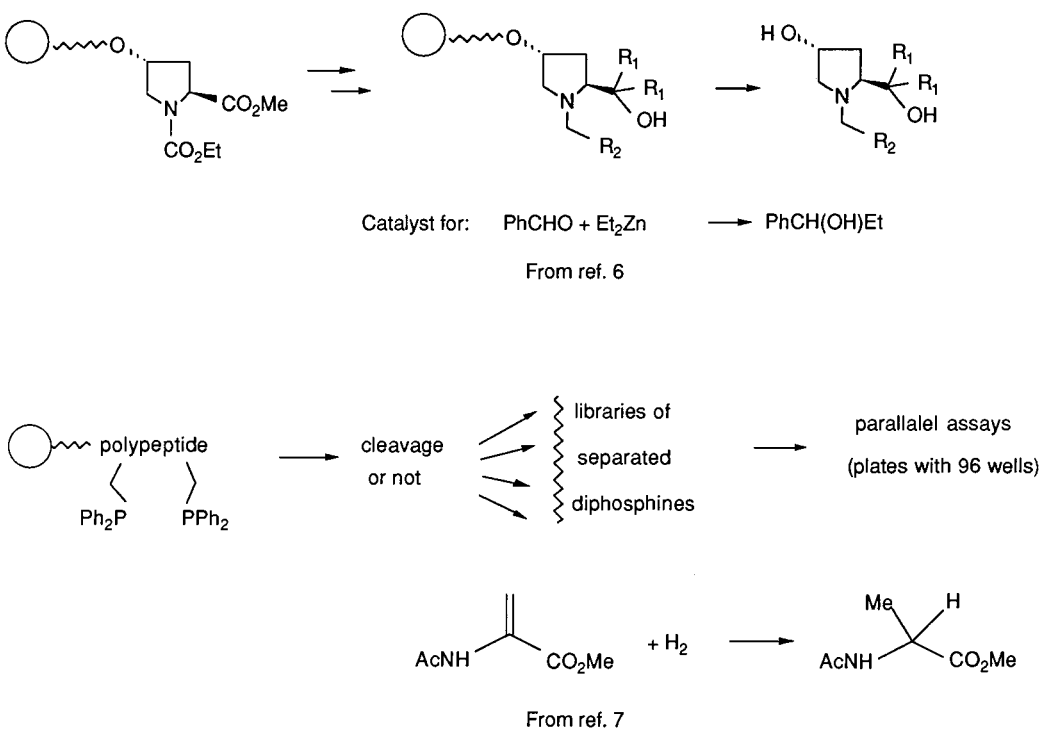




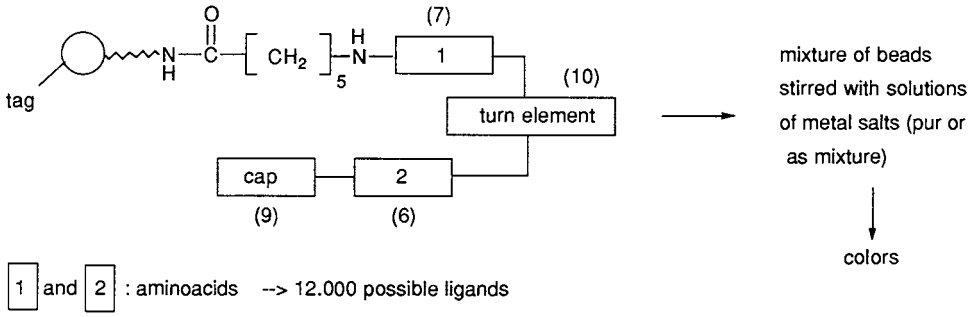
Scheme 3. Optimization of 'modular' chiral ligands for catalysis (from ref. [8]).

These isolated compounds were used as catalysts for the addition of diethylzinc on benzaldehyde, ee's up to 94% have been obtained.

Gilbertson et al. [7] in an exploratory research prepared diphosphines derived from polypeptides (Scheme 2). The solid-phase peptide synthesis was used. A supported rhodium complex was generated from a diphosphine (12-residue peptide) and catalyzed hydrogenation of methyl ester of *N*-acetyl dehydroalanine.



Scheme 2. Synthesis of libraries of chiral ligands by combinatorial chemistry.



Scheme 4. Research of metal chelates, potential precursors of catalysts (from ref. [10]).

Hoveyda et al. [8] used a dipeptide as the core in the construction of a 'modular' chiral salen (Scheme 3). In this combinatorial approach some dipeptides were prepared bound to a resin and transformed into corresponding Schiff bases. These dipeptide can be prepared efficiently in a parallel manner and transformed into the corresponding Schiff bases by reaction with aromatic aldehydes. About 20 ligands may be prepared daily. These insoluble ligands and one equivalent amount of $Ti(OiPr)_4$ are catalysts for the opening of *meso* epoxides such as epoxycyclohexane by TMSCN. However more reliable results were obtained on the homogeneous ligands (methyl esters) generated after cleavage from the polymer support. Each of the three modules of the ligands were successively studied and their structure optimized. By this quite fast way a good ligand 2 has been discovered. The strategy assumed additive effects of the substituents. This is a first approximation since in some cases cooperative effects can arise.

Still et al. [9] described encoded solid-phase libraries of potential metal ion binders. A cyclen macrocyclic tetraamine was the core with binding properties toward divalent transition metals. Substituents on three nitrogens were oligopeptides. One nitrogen was used for attachment to the resin. Libraries up to 10^5-members have been prepared. Colored tests on the beads allowed to discover excellent binders of Cu^{2+}.

Jacobsen et al. [10] used a similar approach to identify novel chiral coordination complexes potentially useful in asymmetric catalysis. Modular ligands (four sections connected to each other) were prepared on a bead (Scheme 4). Sections 1 and 2 are aminoacids and are connected together by a turn element (proline or some β-aminoalcohols). The last element of the molecule is a end cap (an acyl group). By combinatorial chemistry it is possible to produce 12000 different ligands. Moreover these ligands were obtained on encoded polystyrenes in order to identify the ligands. The ability of these potential ligands to form coordination complexes was tested by shaking a mixture of beads with an homogeneous solution of some selected metal ions. For example a library (10 mg) of 24000 beads was treated by a solution of a given concentration of Ni(II), rinsed and treated by dimethylglyoxine in methanol. A reddish-pink precipitate on some beads immediately indicated which one had strong affinity to Ni(II), for the Ni(II) concentration used. By this approach some families of selective and powerful binders of Ni(II) or other metal ions were discovered.

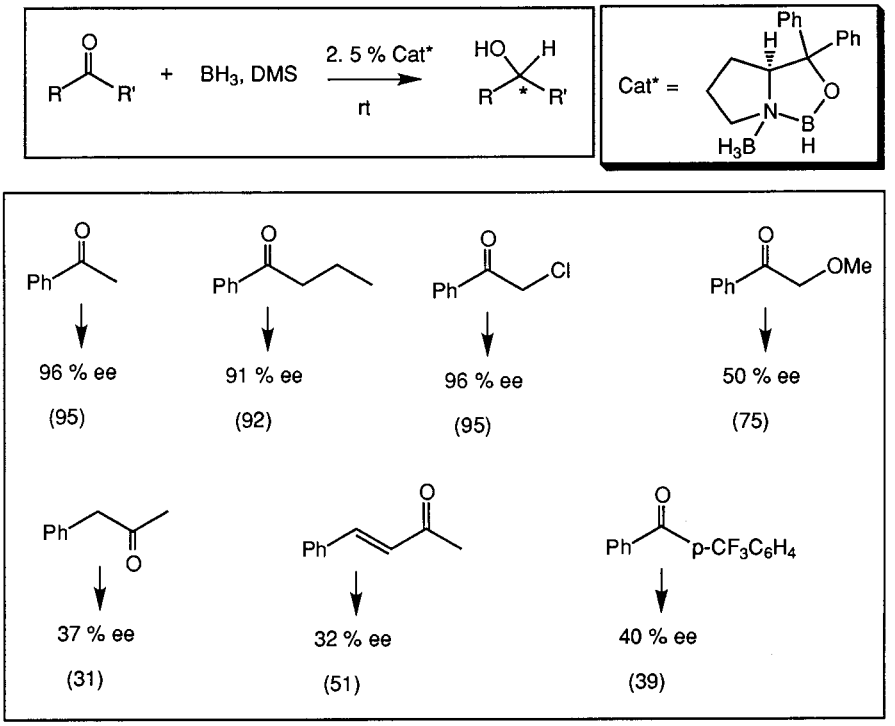
In conclusion the multi-component reactions combined to solid-phase synthesis is an excellent approach to create a wide range of chiral ligands.

5. The one-pot multi-substrate screening

We recently developped the concept of fast screening of a given chiral catalyst by carrying out the reaction in presence of a set of different substrates [11]. The reaction may in principle be valid if the products do not interfere with the catalyst (no autoinduction). The ideal conditions would be to analyze the ee of products arising of a large amount of prochiral substrates. In fact there are limitations in the analytical methods because of some overlaps in the elution of the various compounds.

We selected asymmetric reduction of ketones by diborane catalyzed by an oxazaborolidine [12] as a test. We used HPLC (chiral phase: Daicel Chiralcel OD-H) to measure the enantiomeric excesses of alcohols. For example a small library such as the one depicted in Scheme 5 correctly reproduced the enantioselectivities of reduction (in parentheses) performed on individual ketones.

For some asymmetric reactions the above approach needs to be considered with caution, especially for reactions where the ee is conversion dependent or where there is some autoinduction. However the simplicity of this method makes it very convenient for a preliminary evaluation of a chiral reagent or catalyst. It could be also used in the parallel screening of chiral auxiliaries prepared by combinatorial chemistry.



Scheme 5. One-pot multi-substrate screening of an asymmetric catalyst (from ref. [11]).

6. Conclusion

In asymmetric catalysis one must no more ignore the modern methods of combinatorial chemistry and fast screening. It will be obviously useful to optimize quickly the structure of a chiral ligand composed of several fragments linked together. However it remains to be established if completely new and original ligands will be discovered by this approach.

References

[1] Some reviews on combinatorial chemistry: refs. [2,3].
[2] F. Ballkenhol, C. von dem Bussche-Hunnefeld, C. Lansky, C. Zachel, Angew. Chem. Int. Ed. Engl. 35 (1996) 2288.
[3] A.W. Czarnik (Guest Ed.) Acc. Chem. Res. (special issue on combinatorial chemistry) 79 (3) (1996) 112.
[4] H.C. Kolb, M.S. Van Nieuwenhze, K.B. Sharpless, Chem. Rev. 94 (1994) 2483.
[5] K. Burgess, H.S. Lim, A.M. Porte, G.A. Sulikowski, Angew. Chem. Int. Ed. Engl. 35 (1996) 220.
[6] G. Lin, J.A. Ellman, J. Org. Chem. 60 (1995) 7712.
[7] S.R. Gilbertson, X. Wang, G.S. Hoge, C.A. Krug, J. Scharfer, Organometallics 15 (1996) 4678.
[8] B.M. Cole, K.D. Shimizu, C.A. Krueger, J.P.A. Harrity, M.L. Snapper, A.H. Hoveyda, Angew. Chem. Int. Ed. Engl. 35 (1996) 1668.
[9] M.T. Burger, W.C. Still, J. Org. Chem. 60 (1995) 7382.
[10] M.B. Francis, N.S. Finney, E.N. Jacobsen, J. Am. Chem. Soc. 118 (1996) 8983.
[11] X. Gao, H.B. Kagan, Chirality 10 (1998) 120.
[12] E.J. Corey, R.K. Bakshi, S. Shibati, J. Am. Chem. Soc. 109 (1987) 5551.