Pure Appl. Chem., Vol. 77, No. 7, pp. 1251–1257, 2005.
DOI: 10.1351/pac200577071251

Combinatorial approach to the discovery of chiral catalysts for asymmetric reactions*

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Abstract: The powerfulness of a combinatorial approach in the discovery of novel chiral catalyst systems, particularly for the development of highly efficient, enantioselective, and practical catalysts for asymmetric reactions, was demonstrated by screening modular chiral catalyst libraries created by the strategy of two-component ligand modification of metal ions on the basis of molecular recognition and assembly.

Keywords: asymmetric catalysis; combinatorial chemistry; titanium; zinc; hetero-Diels–Alder reaction.

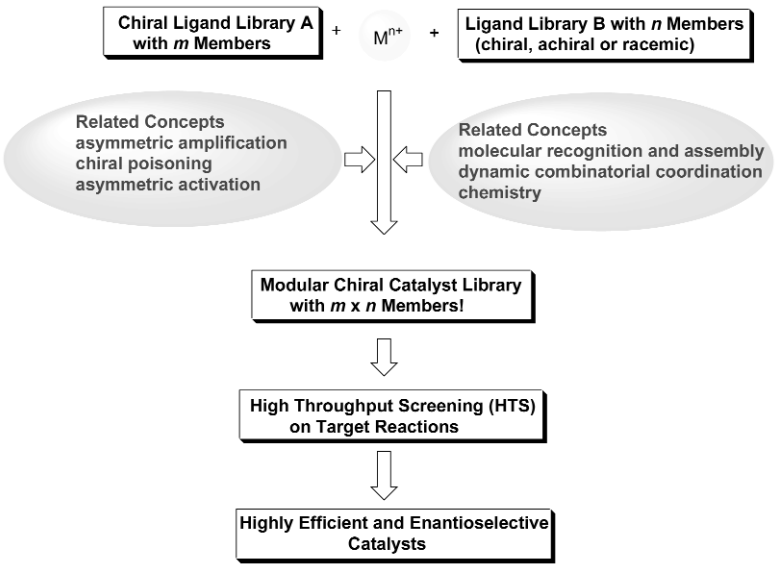
INTRODUCTION

To achieve maximum chiral multiplication, chemists must create efficient catalytic systems that permit precise discrimination among enantiotopic atoms, groups, or faces in achiral molecules [1]. The candidates for these enantioselective catalysts are often metal complexes bearing chiral and nonracemic organic ligands, often in enantiopure form. Therefore, tuning the catalyst to achieve the perfect match among chiral ligand, metallic ion, substrate, and so on is a key point for achieving the maximum chiral multiplication. Combinatorial chemistry has been well recognized as a powerful strategy for the discovery and optimization of bioactive drugs, novel coordination complexes, and solid-state materials [2]. High diversity and efficiency can be regarded as two distinguishing advantages of the combinatorial chemistry approach. Successful catalyst optimization requires rational design, intuition, and experience, but also some degree of trial and error. Therefore, the generation of a combinatorial library of chiral metallic complexes and the screening of the set of constituents of the library for the target reaction by taking advantage of its high diversity and efficiency would provide a potentially powerful approach for the discovery of highly efficient and enantioselective catalysts [3]. In the present paper, we will discuss the principle and application of a combinatorial approach to the engineering and screening of chiral catalysts for asymmetric catalysis.

PRINCIPLE FOR CHIRAL CATALYST LIBRARY ENGINEERING

The principle of the combinatorial chemistry approach to chiral catalyst discovery for asymmetric catalysis can be considered as a parallel analog of the combinatorial chemistry approach for drug discovery. As shown in Scheme 1, the generation of a dynamic combinatorial library of chiral metallic complexes

Pure Appl. Chem.* **77, 1087–1296. An issue of reviews and research papers based on lectures presented at the 15th International Conference on Organic Synthesis (ICOS-15), held in Nagoya, Japan, 1–6 August 2004, on the theme of organic synthesis.



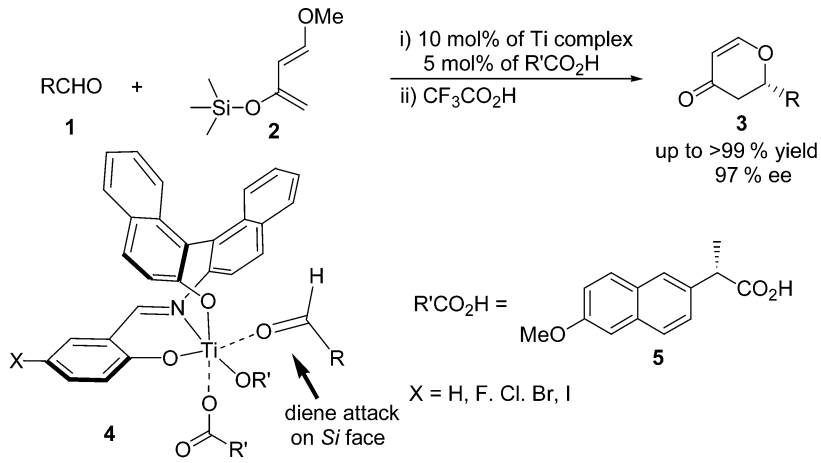
Scheme 1

and the expression of the constituents of library in the target reaction should be a convenient approach to the discovery of efficient chiral catalysts. Moreover, including two different ligands in the catalyst system would make the reaction more active and selective on the basis of "asymmetric activation" [4] and "ligand acceleration" [5] concepts. The other advantage of this approach includes the ease of generating a larger extent of catalyst diversity in the library, which will make the fine-tuning of electronic and steric effects of catalysts more conveniently to achieve high activity and enantioselectivity of the catalysis. This strategy is closely related to the concepts of asymmetric amplification, chiral poisoning, asymmetric activation, as well as molecular recognition, molecular assembly, and dynamic combinatorial coordination chemistry in which the interaction and recognition among chiral ligands, metallic ion, and substrate, as well as the aggregation and the deaggregation of the assemblies, are reversible and dynamic in principle [6]. The goal of channeling the catalysis through one particular complex is usually achieved by an overwhelming kinetic activity favoring that one complex over the many other complexes that are assembled in solution.

DISCOVERY OF TRIDENTATED TITANIUM CATALYSTS FOR ENANTIOSELECTIVE HDA REACTION THROUGH LIGAND AND ADDITIVE DIVERSITY: DRAMATICALLY SYNERGISTIC EFFECT OF CARBOXYLIC ACID ADDITIVE AND POSITIVE NONLINEAR EFFECT

Enantioselective hetero-Diels–Alder (HDA) reaction between aldehydes (**1**) and Danishefsky's diene (**2**) has provided powerful access to 2-substituted 2,3-dihydro-4*H*-pyran-4-one (**3**), a type of heterocycle with extensive applications for natural and unnatural product synthesis [7]. During the course of our study on the catalysis of HDA reaction with tridentate titanium complexes, we discovered a group of highly efficient chiral tridentate titanium catalysts for HDA reaction of Danishefsky's diene and a variety of aldehydes through ligand and additive diversity [8]. The research was inspired by a serendipitous discovery that the presence of benzoic acid could dramatically improved the activity and enantioselectivity of the titanium complex (**4**) catalyzed HDA reaction. On the basis of this observation, a library of tridentate Schiff's base ligands with 22 members and a library of acid additives with 36 components were set up, respectively. In principle, 792 (22×36) different catalysts could be made from the combinations of chiral ligands and acid additives in the presence of titanium isoproxide. However, to control

the number of the catalysts synthesized and screened, a representational search strategy [3a] was employed. While achiral carboxylic acid 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, **5**), and as a result, up to quantitative yield and 97 % ee of the product could be obtained (Scheme 2).



Scheme 2

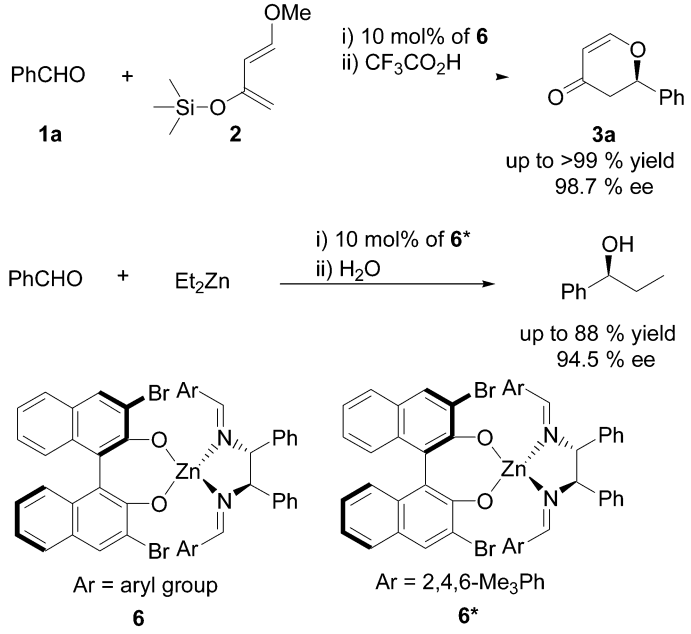
Quantitative study on the effect of chiral carboxylic acid revealed that the reaction could be accelerated at one order of magnitude. Another interesting feature of the present catalytic system was the existence of significant positive nonlinear effect, which indicated that the heterochiral Schiff's base–titanium complexes may have higher stability than their homochiral counterparts. As a result, the homochiral Schiff's base–titanium complexes with higher ee than that of starting ligand will react with carboxylic acid additive to form the more active species and predominate the catalytic process. The successful isolation and characterization of heterochiral [(±)-**L**]$_2$Ti and enantiopure [(*R*)-**L**]$_2$Ti complexes have also strongly supported the explanation for activation effect of carboxylic acid additive and positive nonlinear effect observed in the catalytic system [9].

ONE CHIRAL CATALYST FOR TWO DISTINCT ENANTIOSELECTIVE REACTIONS: KILLING TWO BIRDS WITH ONE METALLIC STONE

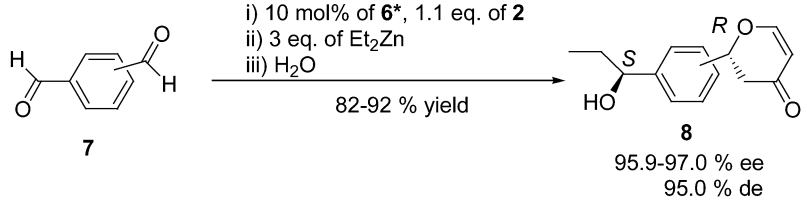
Mikami and coworkers have demonstrated the success of the combinatorial approach to the discovery of highly efficient and enantioselective catalysts for addition of diethylzinc to aldehydes via screening the catalyst libraries generated by a combination of small chiral ligand and activator libraries [10]. We found that the catalyst prepared by combination of (*R*)-BINOL with diimine in the presence of $ZnEt_2$ could promote the HDA reaction of Danishefsky's diene with benzaldehyde at 0 °C to give (*S*)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one in good yield and moderate enantioselectivity (63.6 % ee) [16]. On the basis of this leading result, a library of activated catalysts was set up to further improve the enantioselectivity of the reaction by tuning the steric and electronic modifications in the diol ligands and diimine activators through a parallel combinatorial approach. Accordingly, a library of chiral diol ligands (with 12 members), including commercially available or easily prepared BINOL and biphenol derivatives, and a library of diimines (with 20 members), derived from enantiopure 1,2-diaminocyclohexane, were created. High-throughput screening of the chiral Zn catalyst library (240 members) generated by assembling the members of diol ligand and diimine activator libraries with Zn showed that all of the catalysts could promote the HDA reaction of benzaldehyde with

Danishefsky's diene at 0 °C to give the desired product **3a**. It was found that complex **6** containing a variety of diimine activators is particularly effective for the reaction, affording adduct **3a** in up to quantitative yield and 94.2 % ee. Under the optimized conditions (–20 °C), adduct **3a** could be obtained in quantitative yield with up to 98.7 % ee [11].

As an effort to explore such a single catalyst that is workable for two distinct asymmetric reactions, the combinatorial approach was again employed to further optimize the activated Zn catalysts **6** for diethylzinc addition to benzaldehyde (Scheme 3). After screening, complex **6*** was found to be the best catalyst for diethylzinc addition to benzaldehyde, to afford (*S*)-1-phenyl-1-propanol with 72 % ee at 0 °C. The enantioselectivity of the reaction could be improved to 94.5 % at a lower reaction temperature (–20 °C) (Scheme 3). Reexamination of catalyst **6*** for HDA reaction of benzaldehyde and Danishefsky's diene at –20 °C resulted in the formation of (*R*)-**3a** with 97.4 % ee and quantitative yield. Therefore, this catalyst system provided an excellent opportunity to conduct two asymmetric reactions in one pot using a single catalyst. The dialdehydes, **7**, terephthalaldehyde and isophthalaldehyde, were then submitted as the substrates to sequential asymmetric HDA reaction and diethylzinc addition to generate dihydropyranone and secondary alcohol moieties in one substrate. As shown in Scheme 4, two asymmetric reactions proceeded efficiently and selectively to give product **8** in 82–89 % yields with 95.9–97.0 % ee and 95.0 % diastereoselectivity [11b]. This research clearly demonstrated the ability of a single catalyst to promote two distinct enantioselective reactions in one pot, which might provide a new direction to the design of chiral catalysts for asymmetric synthesis.



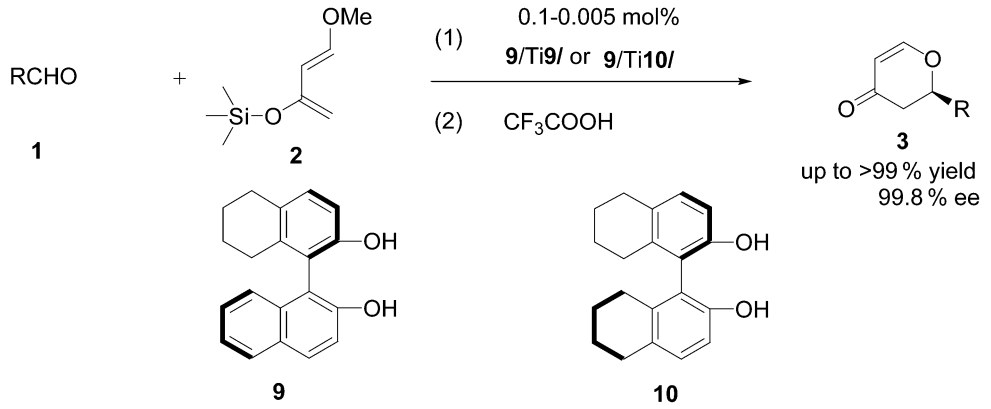
Scheme 3



Scheme 4

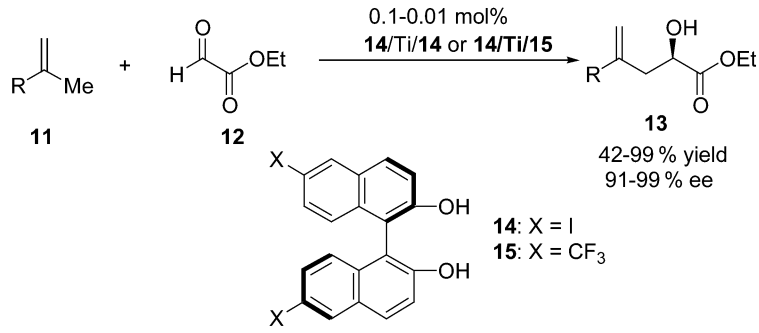
DISCOVERY OF EXCEPTIONALLY EFFICIENT CHIRAL CATALYSTS FOR ENANTIOSELECTIVE HDA AND CARBONYL ENE REACTIONS THROUGH A COMBINATORIAL APPROACH

Although the enantioselectivity of up to 99 % has been achieved in the HDA reaction of aldehydes with Danishefsky's diene using various chiral Lewis acids, a major drawback of these catalytic systems has been their high catalyst loadings (1–10 mol %) [7]. The development of exceptionally active and enantioselective catalysts for HDA reaction is particularly important in terms of practical consideration. We have recently described the development of exceptionally efficient enantioselective catalysts for solvent-free HDA reaction by high-throughput screening of dynamic combinatorial libraries of chiral titanium complexes. It was found that titanium complexes of H_4-BINOL (**9**) and H_8-BINOL (**10**) were extremely efficient for this reaction, especially under solvent-free conditions, to afford dihydropyrone derivatives with up to quantitative yield and 99.8 % ee (Scheme 5). Particularly, in the cycloaddition of furfural to Danishefsky's diene, 0.005 mol % of 9/Ti/10 could promote the reaction to give the corresponding cycloadduct in 63 % yield with 96.3 % ee. Therefore, the present catalytic system provides an attractive protocol to various optically active dihydropyrones in terms of the following features: (i) the chemicals are all inexpensive and easily available; (ii) the protocol has a broad scope of substrates; (iii) the reaction shows enhanced enantioselectivity when the amount of catalyst is reduced; (iv) the reaction is environmentally benign and energy-saving because of solvent-free and room-temperature reaction conditions; (v) exceptionally low catalyst loading (0.1–0.005 mol %) is sufficient to achieve high yields and optical purities of the products [12].



Scheme 5

As a continuous effort for the development of practical asymmetric catalysis of organic reactions, we have successfully discovered two highly efficient and enantioselective catalysts for a quasi-solvent-free carbonyl ene reaction using combinatorial approach. The reaction of ethyl glyoxylate with a variety of olefins could be accomplished using 0.1–0.01 mol % of catalysts to give α-hydroxy esters in good to excellent yields with up to 99 % ee (Scheme 6) [13].



Scheme 6

CONCLUSION

We have attempted to show the principle and application of a combinatorial approach in the discovery of chiral catalysts for enantioselective reactions. The concept is focused on the creation of a modular chiral catalyst library using two-component ligand modification strategy on the basis of molecular recognition and assembly. The self-assembled chiral catalyst using two different ligands indeed exhibited the synergistic effect in terms of both enantioselectivity and activity in comparison with its corresponding homocombinations in some cases. It can be expected that more efficient and enantioselective catalysts, as well as unprecedented classes of catalysts or catalytic reactions, will be discovered in the future with the help of a combinatorial chemistry approach. We hope that the strategy described in this paper will stimulate further research on the application of a combinatorial approach in asymmetric catalysis.

ACKNOWLEDGMENTS

We are grateful to the NSFC, CAS, the Major Basic Research Development Program of China (grant no. G2000077506), and the Ministry of Science and Technology of Shanghai Municipality for financial support of this project.

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