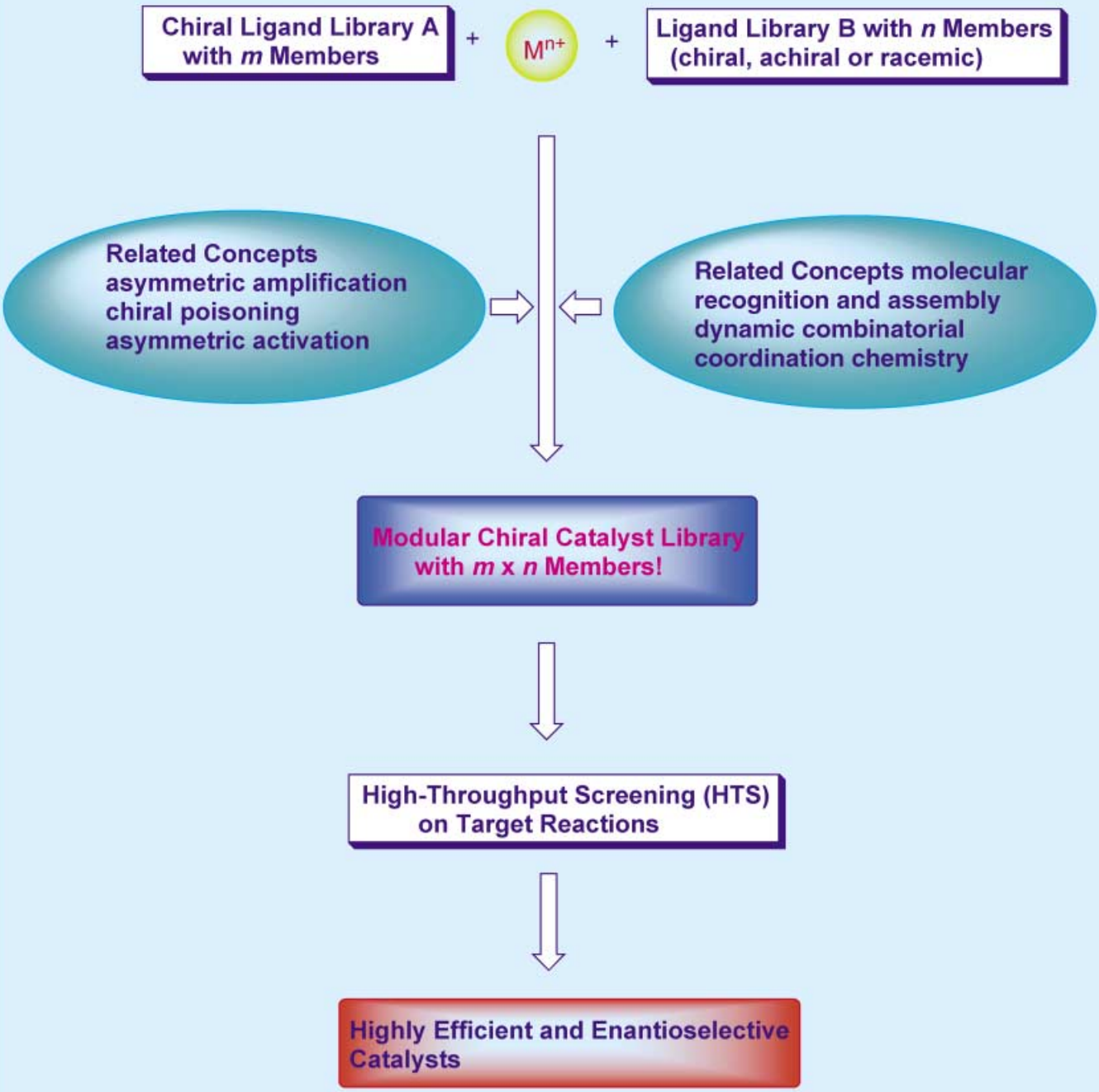
Combinatorial Approach to Chiral Catalyst Engineering and Screening



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Combinatorial Chemistry Approach to Chiral Catalyst Engineering and Screening: Rational Design and Serendipity

Kuiling Ding,* Haifeng Du, Yu Yuan, and Jiang Long[a]

Abstract: An efficient asymmetric catalyst relies on the successful combination of a large number of interrelated variables, including rational design, intuition, persistence, and good fortune—not all of which are necessarily well-understood; this renders such practice largely empirical. As a result, the possibility of using combinatorial chemistry methods in asymmetric catalysis research has been widely recognized to be highly desirable. In this account, we attempt to show the principle and application of combinatorial approach in the discovery of chiral catalysts for enantioselective reactions. The concept focuses on the strategy for the creation of a modular chiral catalyst library by two-component ligand modification of metal ions on the basis of molecular recognition and assembly. The self-assembled chiral catalyst with two different ligands indeed exhibited synergistic effects in terms of both enantioselectivity and activity in comparison with its corresponding homocombinations in many reactions. The examples described in this paper demonstrated the powerfulness of combinatorial approach for the discovery of novel chiral catalyst systems, particularly for the development of highly efficient, enantioselective, and practical catalysts for enantioselective reactions. We hope this concept will stimulate further work on the discovery of more highly efficient and enantioselective catalysts, as well as unexpected classes of catalysts or catalytic enantioselective reactions in the future with the help of a combinatorial chemistry approach.

Keywords: asymmetric catalysis · combinatorial chemistry · high-throughput screening · molecular assembly · molecular recognition

[a] Prof. Dr. K. Ding, H. Du, Dr. Y. Yuan, Dr. J. Long
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Road, Shanghai 200032 (P. R. China)
Fax: (+86) 21-6416-6128
E-mail: kding@mail.sioc.ac.cn

Introduction

Molecular chirality (handedness) is a principal element in nature that plays a key role in science and technology.[1] Development of organic reactions to provide enantiomerically enriched products has been recognized as the central importance in pharmaceutical, agricultural, synthetic organic, and natural product chemistry.[2] Among various approaches to optically active molecules, asymmetric catalysis of organic reactions is the most general and efficient process in terms of chirality economy and, hence, an environmentally benign process as well, because it achieves chirality multiplication or chirality amplification, thereby affording a large amount of the enantioenriched product, while producing a small amount of waste material owing to very small amount of chiral catalyst employed. As stated by Noyori, asymmetric catalysis is four-dimensional chemistry. The high efficiency of the reaction can only be achieved through a combination of both an ideal three-dimensional structure (x, y, z) and suitable kinetics (t).[2a] Therefore, development of highly efficient enantioselective catalysts is one of the most challenging endeavours for synthetic organic chemists. To achieve maximum chiral multiplication, chemists must create efficient catalytic systems that permit precise discrimination among enantiotopic atoms, groups, or faces in achiral molecules. The candidates for these enantioselective catalysts are often metal complexes bearing chiral and nonracemic organic ligands, often in enantiopure form. Therefore, tuning the catalysts 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.[3] Between the available split-and-mix and parallel strategies, the latter is more employable for lead optimization, whereby high-throughput screening (HTS) is an essential technique for tuning a variety of modifications. Successful catalyst optimization requires rational design, intuition, and experience, but also some degree of trial and error. It is often the anticipated hit that becomes the key data which result in a successful investigation. With the rising demands

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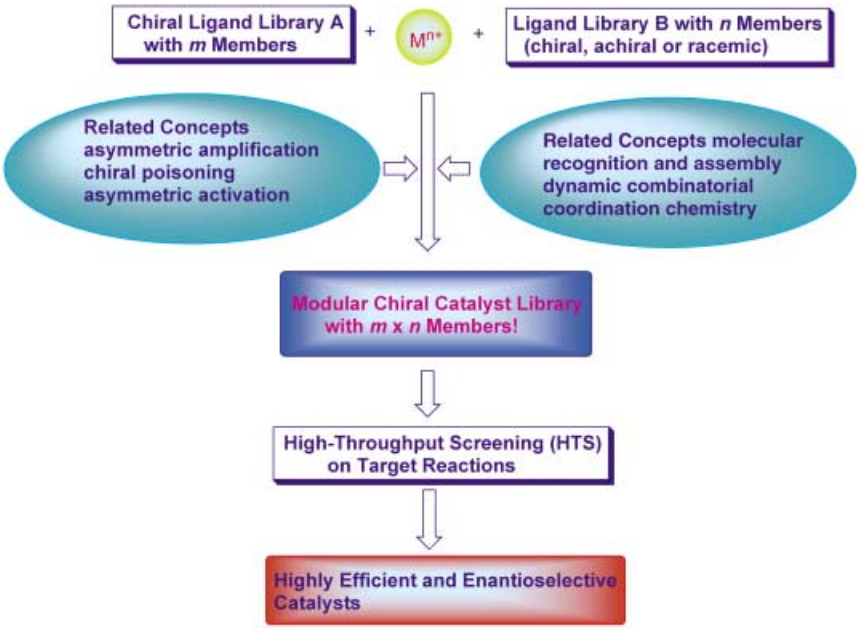
to increase efficiency in research and development, combinatorial chemistry has not only changed the drug discovery process in the pharmaceutical industry, but also significantly affected other research areas of chemistry, such as discovery of more efficient materials and catalysts.[3c,d] Particularly, a similar paradigm, namely combinatorial asymmetric catalysis, is now taking in asymmetric catalysis to speed up the development of this challenging research area.[4] Another important consideration in favor of the creation of chiral catalyst library is with regard to the catalyst's scope and applicability, because there is no such a catalyst that is versatile to all substrates. Therefore, generation of a combinatorial library of chiral metallic complexes and the screening of the set of the constituents of the library for the target reaction by taking its advantages of diversity and high efficiency would provide a potentially powerful approach for the discovery of highly efficient and enantioselective catalysts. In the present paper, we will discuss the principle and application of combinatorial approach to chiral catalyst engineering and screening for asymmetric catalysis.



Scheme 1. The principle for combinatorial asymmetric catalysis: creation of a chiral catalyst library through two-component ligand modification of metal ion.

The Principle of Chiral Catalyst Library Engineering

The principle of combinatorial chemistry approach to chiral catalyst discovery for asymmetric catalysis can be considered as a parallel analogue of combinatorial chemistry approach for drug discovery. High diversity and efficiency are well recognized as the two most important advantages of combinatorial chemistry approach. By taking these advantages, the creation of chiral catalyst library and high-throughput evaluation of the generated library for the target reactions are two key issues in combinatorial asymmetric catalysis. Aside from the traditional chiral HPLC or GC systems with autosamplers, various new approaches of high-throughput *ee* assays for enantioselective catalysts and enzymes have been developed since 1997; these make the highly efficient evaluation of the chiral catalyst library possible.[5] The combinatorial asymmetric catalysis based on the modular ligand diversity has also achieved significant development.[4] This paper will not discuss the stories of these two aspects and the attention of this account will be focused on the strategy for the creation of modular chiral catalyst library, another key issue of combinatorial asymmetric catalysis, on the basis of molecular recognition by combination of two different ligands with metallic ions (Scheme 1).

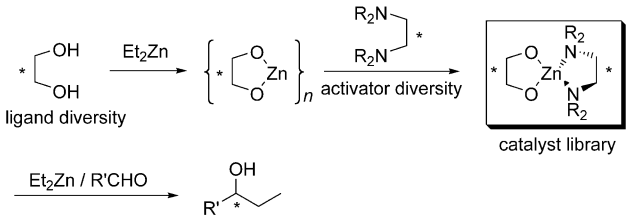
Recently, "asymmetric amplification",[6] "chiral poisoning",[7] "asymmetric activation",[8] "ligand-accelerated catalysis",[9] "chiral environment amplification",[10] and "asymmetric autocatalysis"[11] concepts have been the interesting topics in asymmetric catalysis. These strategies are closely related to the concepts of molecular recognition, molecular assembly, and dynamic combinatorial libraries, 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.[12] The goal of channeling the catalysis through one particular complex is usually achieved by an overwhelming kinetic activity favoring one complex over the many other complexes that are assembled in solution. Therefore, generation of a dynamic combinatorial library of chiral metallic complexes and the expression of the set of constituents of library in the target reaction should be a potentially powerful approach for the discovery of highly efficient enantioselective catalysts. Moreover, including two different ligands in the catalyst system would make the reaction more active and selective on the basis of "asymmetric activation"[8] and "ligand acceleration"[9] concepts. The other advantage of this approach includes the ease of generating larger extent of catalyst diversity in the library (Scheme 1), which will make the fine tuning of electronic and steric effect of catalysts more convenient in order to achieve high activity and enantioselectivity of the catalysis.

Engineering the Chiral Catalyst Library through Asymmetric Activation

According to asymmetric activation concept, a chiral molecule (activator) is not only able to selectively activate one enantiomer of a racemic chiral catalyst to afford optically

active product, but it is also to make the enantiopure catalyst be even more efficient in terms of producing a greater enantiomeric excess in the product than can the enantiomerically pure catalyst on its own.[8] On the basis of this concept, Mikami and co-workers have demonstrated the success of combinatorial approach to the discovery of highly efficient and enantioselective catalyst for addition of diethylzinc to aldehydes by screening the catalyst libraries generated by combination of small chiral ligand and activator libraries.[13] It is reasonable to assume that the active catalyst in the addition of diethylzinc to aldehydes is a monomeric zinc alkoxide, and the cleavage of the higher aggregates will result in an activation of overall catalyst system.[14] As shown in Scheme 2, for the activation of the diol–zinc catalyst system, the addition of a chiral nitrogen ligand is the most efficient way, because of its strong ability to coordinate with zinc cation.[15]

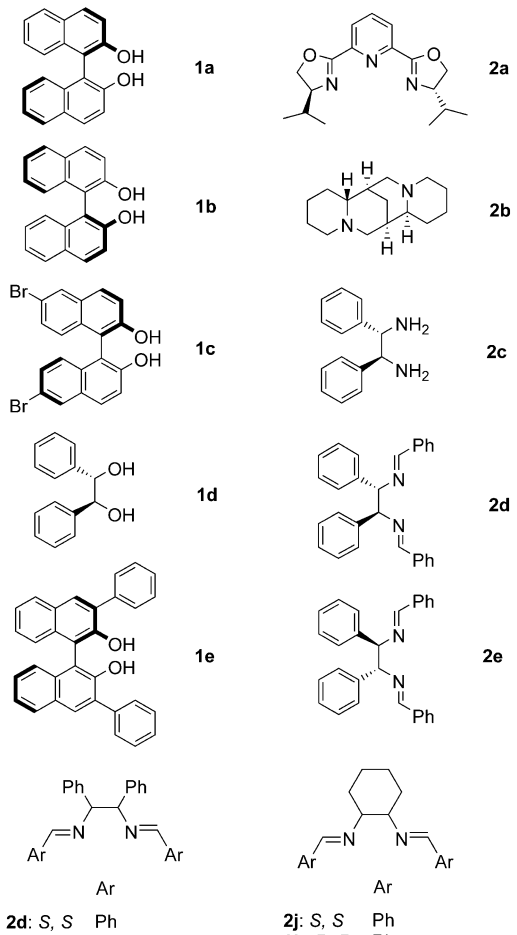
Combination of a small library of chiral diol ligands (**1a**–**1e**, Scheme 3) and chiral activators (diamines or diimines, **2a**–**2e**) in the presence of diethylzinc results in formation of



Scheme 2. The principle for generation of a chiral Zn catalyst library on the basis asymmetric activation concept.

a primary catalyst library, which was then screened for enantioselective addition of diethylzinc to benzaldehyde by HPLC-CD technique.[13] The enantioselectivity of the reaction was increased by matched combination of diol ligands and nitrogen activators. For example, **1b** and **2d** promoted the reaction to give (*S*)-1-phenyl-1-propanol with 8.2% *ee* (54% yield) and 1.1% *ee* (64% yield), respectively. However, the combined use of **1b** and **2d** quantitatively provided the product with 37.4% *ee* (*S*). The best combinations from the primary combinatorial library were found to be **1e**/**2d** and **1e**/**2e** to afford (*S*)-1-phenyl-1-propanol with up to 65% *ee* and in quantitative yields.

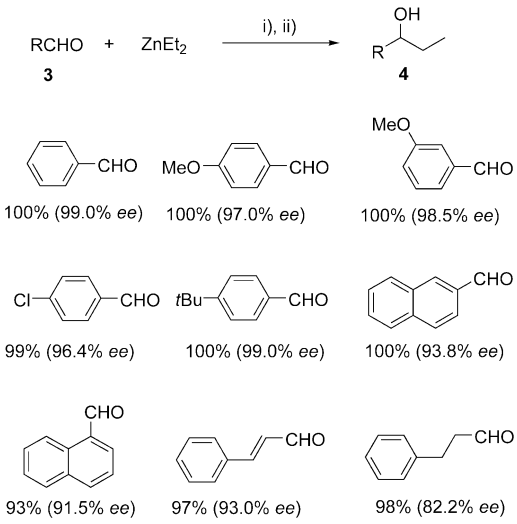
On the basis of these leading results, a new library of diimine activators with 12 members (**2d**–**2o**, Scheme 3) was then prepared. It was found that all library members (**2d**–**2o**) significantly activate the Zn–**1e** complex and produce 1-phenyl-1-propanol in higher yields and enantioselectivities than those obtained by only using the ligand **1e** or activators (**2d**–**2o**) themselves. The best combination discovered was **1e**/**2i**, which was further optimized by lowering the reaction temperature to −78°C (99% *ee*, quantitative yield). Under the optimized conditions, **1e**/**2i** proved to be extremely effective and enantioselective (up to 100% yield and 99% *ee*) for the addition of diethylzinc to a range of aldehydes (**3**) (Scheme 4).[13]



2d: *S, S* Ph
2e: *R, R* Ph
2f: *S, S* 2,6-$Cl_2C_6H_3$
2g: *R, R* 2,6-$Cl_2C_6H_3$
2h: *S, S* 2,4,6-$Me_3C_6H_2$
2i: *R, R* 2,4,6-$Me_3C_6H_2$

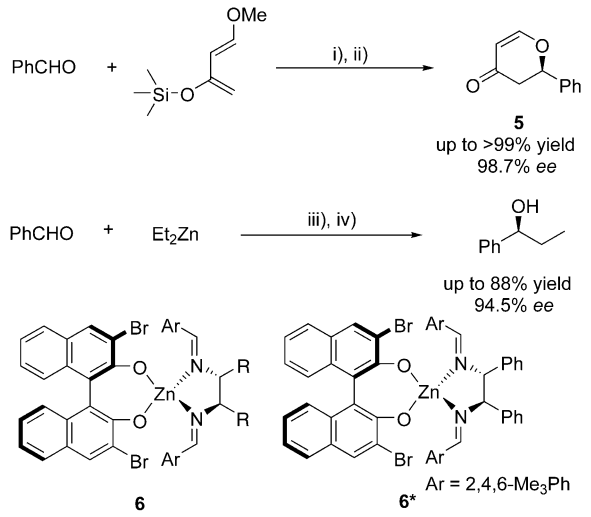
2j: *S, S* Ph
2k: *R, R* Ph
2l: *S, S* 2,6-$Cl_2C_6H_3$
2m: *R, R* 2,6-$Cl_2C_6H_3$
2n: *S, S* 2,4,6-$Me_3C_6H_2$
2o: *R, R* 2,4,6-$Me_3C_6H_2$

Scheme 3. Libraries of chiral ligands (**1a**–**e**) and chiral activators (**2a**–**2o**).



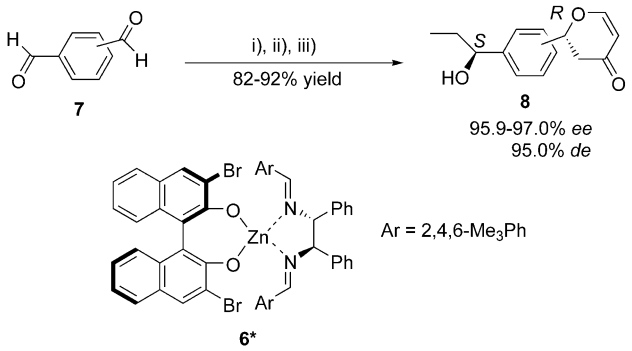
Scheme 4. Asymmetric addition of Et_2Zn to aldehydes in the presence of **1e**/**2i** to provide the secondary alcohols: i) 10 mol% of **1e**/**2i**; in CH_2Cl_2/hexane, −78°C to −20°C; ii) H_2O.

Ding and co-workers found that the catalyst prepared by combination of (*R*)-BINOL (**1a**) with diimine **2d** in the presence of $ZnEt_2$ could promote the hetero-Diels–Alder (HDA) reaction between Danishefsky's diene and benzaldehyde at 0 °C to give (*S*)-2-phenyl-2,3-dihydro-*4H*-pyran-4-one (Scheme 5) 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 **5**. It was found that complex **6** containing a variety of diimine activators is particularly effective for the reaction, affording adduct **5** in up to quantitative yield and 94.2 % *ee*. Under the optimized conditions (−20 °C), adduct **5** could be obtained in quantitative yield with up to 98.7 % *ee*.[16]



Scheme 5. Asymmetric catalysis of HDA and diethylzinc addition reactions by using activated zinc catalysts: i) 10 mol % of **6**; ii) CF_3CO_2H; iii) 10 mol % of **6***; iv) H_2O.

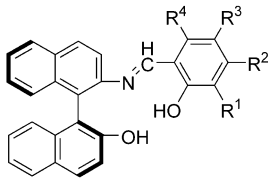
As an effort to explore such a catalyst that can be used to catalyze two distinct asymmetric reactions, the combinatorial approach was again employed to further optimize the activated Zn catalysts **6** for diethylzinc addition to benzaldehyde (Scheme 5). After screening, the complex **6***, containing activator **2i**, was the best catalyst for diethylzinc addition to benzaldehyde and afforded (*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 5). Reexamination of catalyst **6*** for HDA reaction of benzaldehyde and Danishefsky's diene at −20 °C resulted in the formation of (*R*)-**5** with 97.4 % *ee* and quantitative yield. Therefore, this catalyst system provides an excellent opportunity to conduct two asymmetric reactions in one pot using a single catalyst. Two dialdehydes, terephthalaldehyde and isophthalaldehyde (**7**), were then submitted as the substrates to sequential asymmetric HDA reaction and diethylzinc addition to generate dihydropyranone and secondary alcohol moieties in one substrate (Scheme 6). The HDA reactions were first carried out in the presence of 10 mol % of **6*** for 30 h at −20 °C in toluene, and then three equivalents of diethyl zinc were introduced to continue the second step asymmetric addition, under the same experimental conditions without workup of the first HDA reaction product. As shown in Scheme 6, two asymmetric reactions proceeded efficiently and selectively to give product **8** in 82–92 % yields with 95.9–97.0 % *ee* and 95.0 % diastereoselectivity.[16] 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 6. Sequential asymmetric catalysis of a hetero-Diels–Alder reaction and diethylzinc addition by using a single catalyst: i) 10 mol % of **6***, 1.1 equiv of Danishefsky's diene, −20 °C, 30 h; ii) 3 equiv of Et_2Zn, −20 °C, 24 h; iii) CF_3CO_2H.

Recently, Ding and co-workers have also demonstrated the discovery of a group of highly efficient chiral tridentate titanium catalysts for the HDA reaction of Danishefsky's diene and a variety of aldehydes through ligand and additive diversity.[17] The research was inspired by a serendipitous discovery that the presence of benzoic acid could dramatically improve the activity and enantioselectivity of the HDA reaction catalyzed by the titanium/(*S*)-**9a** complex. On the basis of this observation, a library of tridentate Schiff base ligands **9a–v** (Scheme 7) with 22 members and a library of acid additives with 36 components were set up. In principle, 792 (22×36) different catalysts could be made from the combination of chiral ligands and acid additives in the presence of titanium isoproxide. However, to control the numbers of the catalysts synthesized and screened, a representational search strategy[18] was employed.

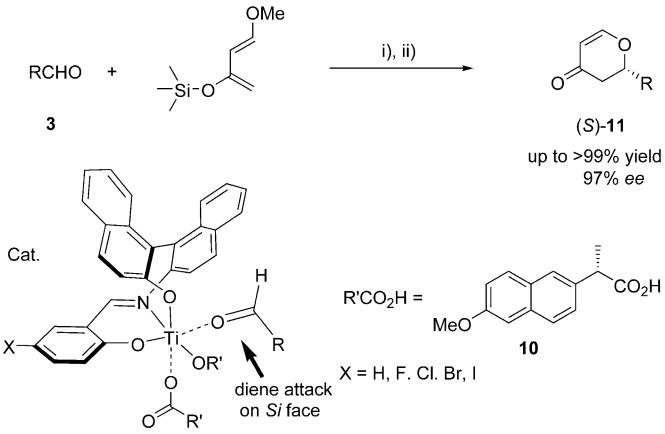
The catalysts prepared from the ligand library (*S*)-**9a–v** were first screened in the presence of benzoic acid and 4 Å molecular sieve (MS) (with a molar ratio of **9**/Ti(O*i*Pr)$_4$/



(*S*)-**9**

(*S*)-**9a**: $R^1 = R^2 = R^3 = R^4 = H$
(*S*)-**9b**: $R^1 = R^3 = Cl$, $R^2 = R^4 = H$
(*S*)-**9c**: $R^1 = R^3 = Br$, $R^2 = R^4 = H$
(*S*)-**9d**: $R^1 = R^3 = I$, $R^2 = R^4 = H$
(*S*)-**9e**: $R^3 = F$, $R^1 = R^2 = R^4 = H$
(*S*)-**9f**: $R^3 = Cl$, $R^1 = R^2 = R^4 = H$
(*S*)-**9g**: $R^3 = Br$, $R^1 = R^2 = R^4 = H$
(*S*)-**9h**: $R^3 = I$, $R^1 = R^2 = R^4 = H$
(*S*)-**9i**: $R^1 = OCH_3$, $R^2 = R^3 = R^4 = H$
(*S*)-**9j**: $R^2 = OCH_3$, $R^1 = R^3 = R^4 = H$
(*S*)-**9k**: $R^3 = OCH_3$, $R^1 = R^2 = R^4 = H$
(*S*)-**9l**: $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$
(*S*)-**9m**: $R^3 = CH_3$, $R^1 = R^2 = R^4 = H$
(*S*)-**9n**: $R^1 = t$Bu, $R^2 = R^3 = R^4 = H$
(*S*)-**9o**: $R^3 = t$Bu, $R^1 = R^2 = R^4 = H$
(*S*)-**9p**: $R^1 = R^3 = t$Bu, $R^2 = R^4 = H$
(*S*)-**9q**: $R^1 = t$Bu, $R^3 = CH_3$, $R^2 = R^4 = H$
(*S*)-**9r**: $R^1 = Br$, $R^3 = CH_3$, $R^2 = R^4 = H$
(*S*)-**9s**: $R^1 = Br$, $R^3 = OCH_3$, $R^2 = R^4 = H$
(*S*)-**9t**: $R^1 = Br$, $R^3 = t$Bu, $R^2 = R^4 = H$
(*S*)-**9u**: $R^1 = OCH_3$, $R^3 = Br$, $R^2 = R^4 = H$
(*S*)-**9v**: $R^3 - R^4 = -(CH)_4-$, $R^1 = R^2 = H$

Scheme 7. A library of tridentate Schiff base ligands.

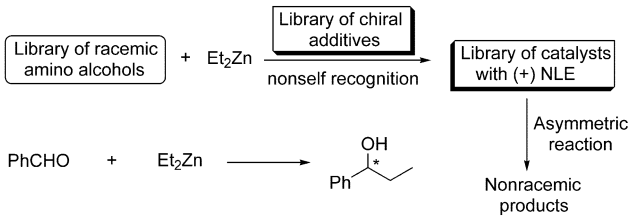


Scheme 8. Development of a group of chiral tridentate titanium catalysts for HDA reaction of Danishefsky's diene and aldehydes through ligand and additive diversity: i) 10 mol% of Ti complex, 5 mol% of **10**; ii) CF_3-CO_2H.

$PhCO_2H$/benzaldehyde = 0.2/0.1/0.05/1). The best results (ee = 85–91%) were obtained using ligands (*S*)-**9a**, (*S*)-**9e–h** and (*S*)-**9m**, which displayed a reduced steric hindrance at the *ortho*-position of the phenol group. Subsequently, a library of 36 carboxylic acid additives, including aromatic, aliphatic, salicylic, amino acids, and others, was then screened to improve the enantioselectivity of the (*S*)-**9a**/Ti-catalyzed HDA reaction. 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, **10**), and as a result, quantitative yield and 97% *ee* of the product could be obtained. To combine the advantages of these two aspects, the catalysts prepared by combination of the superior Schiff base ligands ((*S*)-**9a**, (*S*)-**9e–h** and (*S*)-**9m**) with $Ti(OiPr)_4$ and the best additive **10** in the presence of 4 Å MS were finally evaluated for the reaction at room temperature. It was found that the catalysts derived from (*S*)-**9a** and (*S*)-**9e–h** showed excellent activity and enantioselectivity for the reaction of Danishefsky's diene and benzaldehyde, affording the product in quantitative yields and 93.5–96.9% *ee*. The scope of the reaction was then investigated on a variety of aldehyde substrates using ligands (*S*)-**9a** and (*S*)-**9e–h** in combination with **10** as an additive in toluene in the presence of 4 Å MS at room temperature. Good to excellent enantioselectivity and yield of 2-substituted 2,3-dihydro-*4H*-pyran-4-ones (**11**) were obtained for all substrates.[17] Moreover, the interesting chemistry, such as dramatic activation effect of carboxylic acid and strong positive nonlinear effect, discovered in this catalyst system also lead to the further studies on the insight into the reaction mechanism[19a] and development of a type of highly efficient and enantioselective dendritic catalysts for HDA reaction.[19b] The importance of these contributions might exceed that of discovering the enantioselective chiral catalysts by a combinatorial approach itself (Scheme 8).

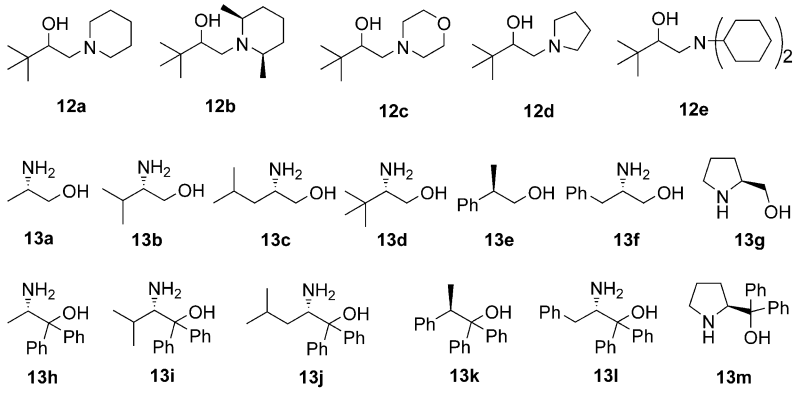
Engineering the Catalyst Library for Enantioselective Addition of Diethylzinc to Aldehydes with Racemic or Achiral Ligands

In the enantioselective addition of diethylzinc to aldehydes, the asymmetric amplification is well recognized to be a consequence of an in situ increase in the *ee* value of the active catalyst, since a racemic ligand is trapped in the more stable, unreactive *meso*-species.[14] In principle, if racemic ligands are used alone, the reaction will definitely give a racemic product. The addition of an alternative nonracemic additive (which should be cheap and easily available) to the racemic catalyst may enantioselectively generate a new species of dinuclear zinc complex with one enantiomer of racemic ligand through "non-self-recognition"[14a] to release the opposite enantiomer of catalyst for asymmetric catalysis (Scheme 9).[20]



Scheme 9. Asymmetric catalysis with racemic amino alcohols in the presence of nonracemic additives.

To exemplify this strategy, Oguni's racemic amino alcohols[21] were chosen to carry out asymmetric catalysis by adding nonracemic additives. Thus, a library of five racemic amino alcohols (**12a–e**, Scheme 10) and a library of optically pure amino alcohols (**13a–m**, Scheme 10) were prepared. The combined use of 10 mol% of racemic amino alcohols ((**12a–e**) and 5 mol% of optically pure additives (**13a–m**) in the presence of diethylzinc afforded a chiral catalyst library of 65 members, which were then evaluated with HPLC-CD technique described above. It was found that **13l** and **13m** showed significant synergistic effect on the enantioselectivity of the reaction. For example, with only **13m** (5 mol%) as a



Scheme 10. Racemic (**12**) and enantiopure (**13**) ligand libraries employed for generating the chiral catalyst library.

chiral inducer, (*R*)-1-phenylpropanol was obtained in 15.6% *ee*. However, the addition of racemic **12a** or **12b** (10 mol%) to the **13m**-catalyzed reaction system resulted in the formation of *S* product in 65.8% and 70.4% *ee*, respectively.[20]

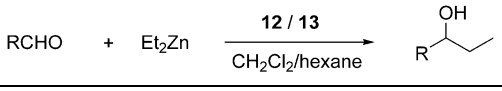
The reactions catalyzed by the better combinations, **12a**/**13l**, **12b**/**13l**, **12a**/**13m**, and **12b**/**13m**, were further optimized by decreasing the reaction temperature to −20°C and −40°C. (*S*)-1-Phenylpropanol could be obtained with up to 92.7% *ee* and in >95% yield under the catalysis of **12a**/**13m** at −40°C. Catalyst combinations **12a**/**13l**, **12b**/**13l**, **12a**/**13m**, and **12b**/**13m** also proved to be effective for the ethylation of a variety of aldehydes under the optimized conditions with 81–92.7% *ee* (Table 1). Both the research on the nonlinear effect in the catalytic systems and that on kinetic behaviors of catalyst combinations (*S*)-**13m**/(*R*)-**12a** and (*S*)-**13m**/(*S*)-**12a** supported the presence of non-self-recognition between **12** and **13**, which demonstrated possibility to carry out the asymmetric reactions with a racemic ligand in the presence of optically pure additive through non-self-recongnition between them.[20]

As we mentioned above, Mikami and co-workers have demonstarted that enantiopure [Zn(3,3′-Ph_2-BINOLate)] species could be activated with enantiopure diimine ligands to form very efficient and enantioselective catalysts for diethylzinc addition to aldehydes.[13] Inspired by this finding, Walsh and co-workers recently reported that achiral diimine or diamine ligands could act as the activators as well in the same catalytic system.[22] The achiral and *meso* ligands that have been screened fall into six distinct classes (Scheme 11):

1) Achiral diimine ligands that do not generate additional chirality on binding to tetrahedral metals (**14a–g**).
2) Diimine ligands with *meso* backbones that have chiral conformations (**15a–g**).
3) Achiral diimine ligands with backbones that become axially chiral on coordination to metal centers (**16a–f**).
4) Achiral diamine ligands that do not form stereocenters on coordination to metal centers (**18a–d**)
5) Achiral diamine ligands that form stereocenters on coordination to metal centers (**19a–d**)
6) Achiral diamine ligands with pendant groups that have axially chiral conformations (**17a–d**).

Thus, employing (*S*)-3,3′-Ph_2-BINOL ((*S*)-**1e**) and a series of achiral diimine and diamine activators in asymmetric addition of diethylzinc to benzaldehyde, the enantiomeric excesses of 1-phenyl-1-propanol between 96% (*R*) and 75% (*S*) have been achieved (Scheme 12), while only 44% *ee* (*S*) of 1-phenyl-1-propanol was obtained in the absence of achiral activator under the experimental conditions. Additionally, the research on the reaction mechanism has also provided insight into the structure and reactivity of these highly enantioselective and efficient Lewis acid catalysts, which supported the original concept (Scheme 2) proposed by Mikami and co-workers.[13]

Table 1. Enantioselectivities for the ethylation of aldehydes with the catalysis by racemic **12** in the presence of optically active **13**: parallel screening of matched substrate/catalyst pairs.

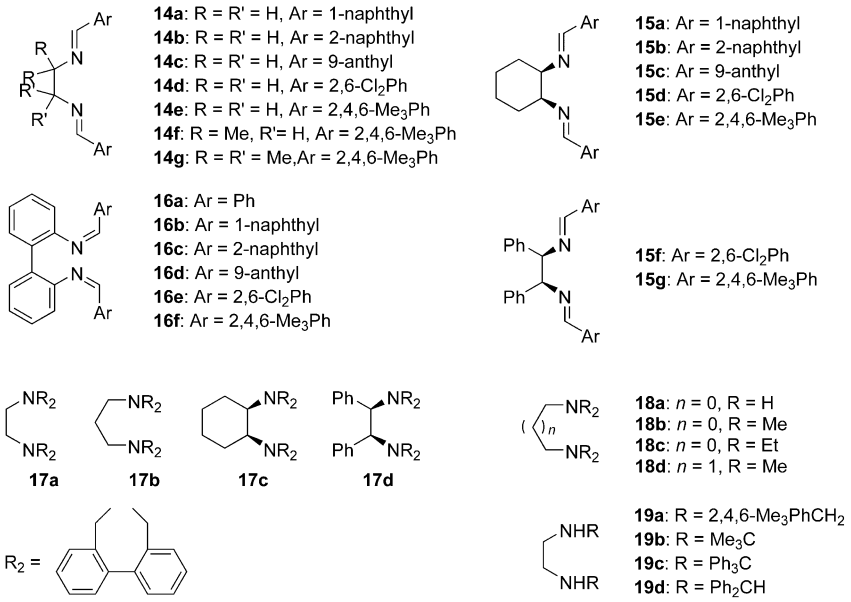


	R	12a/13l	12b/13l	12a/13m	12b/13m
1	Ph (**a**)	86.0	86.1	92.7	90.6
2	*p*-ClC_6H_4 (**b**)	69.9	82.3	84.6	92.1
3	*m*-MeC_6H_4 (**c**)	85.7	81.0	90.1	87.3
4	*p*-$MeOC_6H_4$ (**d**)	87.5	90.3	90.0	91.4
5	*trans*-$C_6H_4CH{=}CH$ (**e**)	67.7	82.3	69.4	69.4
6	*o*-$MeOC_6H_4$ (**f**)	69.8	76.7	74.5	86.3
7	ferrocenyl (**g**)	81.9	90.6	91.7	72.9
8	*p*-$Me_2NC_6H_4$ (**h**)	23.6	55.6	36.2	81.0[a]
9	α-$C_{10}H_7$ (**i**)	69.9	72.2	69.3	86.3
10	*p*-MeC_6H_4 (**j**)	74.7	80.0	82.4	80.0
11	*m*-$MeOC_6H_4$ (**k**)	79.2	80.7	76.9	76.4
12	*p*-BrC_6H_4 (**l**)	76.6	73.6	82.7	79.5
13	*trans*-MeCH=CH (**m**)	78.3	84.4	80.7	84.4

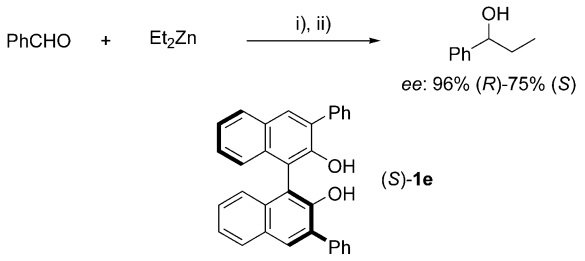
[a] 0°C.

Engineering the Catalyst Library through Homo- and Heterocombination of Two Ligands with Metal Ion: Discovery of Exceptionally Efficient Catalysts for Enantioselective Reactions

Although selectivities of >95% *ee* have been achieved in many catalytic enantioselective reactions, a major drawback of the existed catalytic systems has been their high catalyst loading [substrate/catalyst (S/C) usually <50].[2] Therefore the need for truly efficient and practical synthesis has been one of the greatest challenges for synthetic chemists. Ding and co-workers have recently described the development of exceptionally efficient enantioselective catalysts for solvent-free hetero-Diels–Alder reaction by high-throughput screening of dynamic combinatorial libraries of chiral titanium complexes. On the basis of the "asymmetric activation" con-

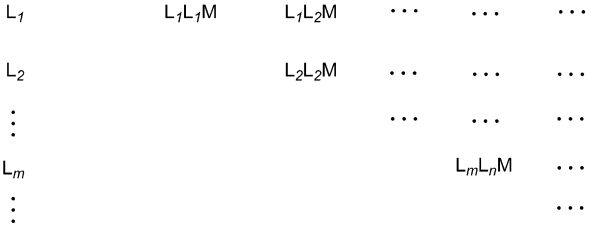


Scheme 11. Achiral diimine and diamine activator library.



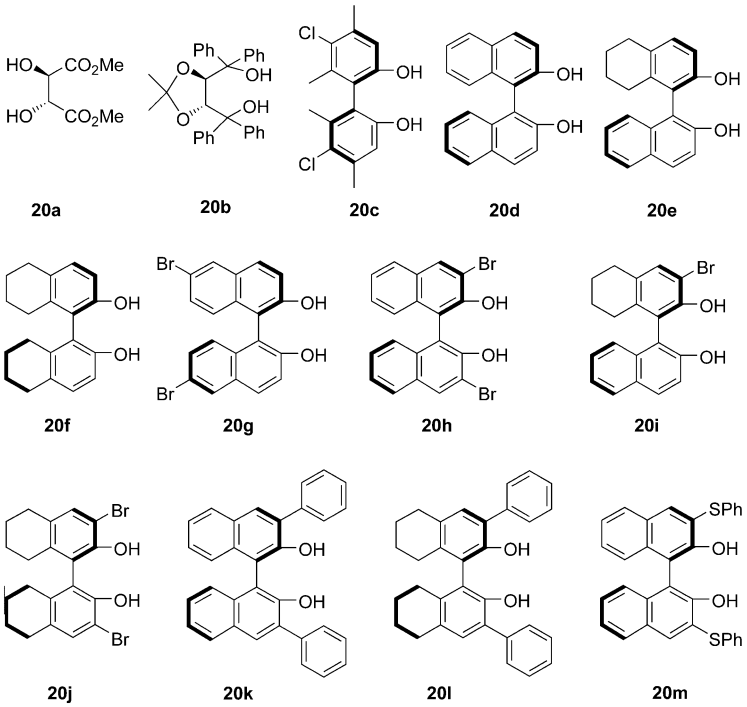
Scheme 12. Asymmetric diethylzinc addition to benzaldehyde catalyzed by [Zn{(*S*)-3,3′-Ph_2-BINOLate}] with the activation of achiral diimine or diamine activators: i) 10 mol% of (*S*)-**1e**/**14–19**, ii) H_2O.

cept,[8] a dynamic combinatorial coordination chemistry strategy[12] was applied to the creation of chiral catalyst library by combining a diol ligand (L_m) with Ti(O*i*Pr)$_4$ and an alternative diol ligand (L_n) in parallel style as shown in Scheme 13. Every member of the library, L_m/Ti/L_n, is actually a mixture of titanium complexes (a smaller library of titanium catalysts), because of the ligand diversity and aggregation feature of titanium complexes.[23] These molecular assemblies form spontaneously, and the composition of the mixtures depends on thermodynamic factors. Therefore, the in situ selection of a highly reactive (and selective) metallic complex from a variety of thermodynamically dictated assemblies by substrate will lead to the highly enantioselective asymmetric catalysis.[24]



Scheme 13. The strategy for generation of a chiral catalyst library through self-assembly of two-component chiral ligands with titanium(IV). L = diol ligand, L_0 means no ligand is added. M = Ti.

A diol ligand library containing 13 members (Scheme 14) was then set up and employed for creating the catalyst library according to the strategy shown in Scheme 13. Thus, a catalyst library containing 104 members could be formed, which were then evaluated for the reaction of Danishefsky's diene with benzaldehyde by using high-throughput chiral HPLC technique. The best combinations identified from the screening were **20e**/Ti/**20e** and **20e**/Ti/**20f**, which afforded the HDA products in very good yields and excellent enantiomeric excesses. The reactions of a variety of aldehydes, including aromatic, olefinic, and aliphatic derivatives, with Danishefsky's diene promoted by the best catalysts (**20e**/Ti/**20e** and **20e**/Ti/**20f**) with only 0.1–0.05 mol% of catalyst loading were found to be highly reproducible, with up to quantitative yield and >99% *ee* (Table 2). Generally speaking, the catalyst generated by heterocombination of **20e** and **20f** demonstrated better per-

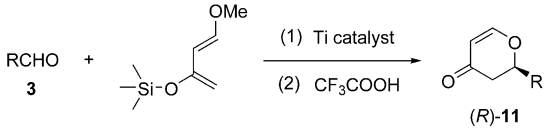


Scheme 14. Chiral ligand library employed for creation of a chiral catalyst library.

formance than that by homocombination of **20e** itself. Particularly, in the cycloaddition of furfural to Danishefsky's diene, 0.005 mol% of **20e**/Ti/**20f** could promote the reaction smoothly 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 following features:

1) The chemicals are all inexpensive and easily available.
2) The protocol has a broad scope of substrates.
3) The reaction shows enhanced enantioselectivity when the amount of catalyst is reduced.
4) The reaction is environmentally benign and energy-saving, because of solvent-free and room-temperature reaction conditions.
5) Exceptionally low catalyst loading (0.1–0.005 mol%) is sufficient to achieve high yield and optical purity of the products.

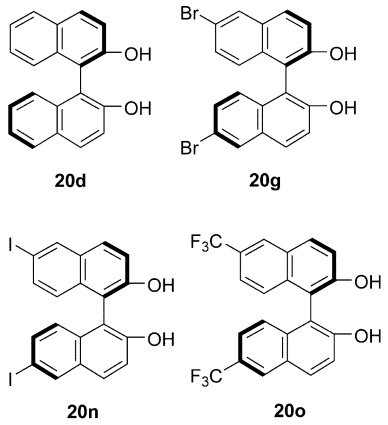
Table 2. Solvent-free asymmetric HDA reaction of aldehydes with Danishefsky's diene.



(*R*)-**11**

	20e/Ti/**20e**				**20e**/Ti/**20f**			
R	Loading [%]	Time [h]	Yield [%]	*ee* [%]	Loading [%]	Time [h]	Yield [%]	*ee* [%]
Ph	0.05	24	>99	99.3	0.05	24	82	99.4
p-$MeOC_6H_4$	0.05	48	>99	90.8	0.05	48	>99	98.0
m-$MeOC_6H_4$	0.05	48	81	96.6	0.05	48	82.6	99.8
o-$MeOC_6H_4$	0.05	48	95	75.1	0.05	48	>99	95.1
3-$PhCH_2CH_2$	0.05	96	>99	97.9	0.05	96	>99	98.3
Trans-PhCH=CH	0.1	96	82	98.4	0.05	96	56.6	96.6
2-furanyl	0.05	48	>99	99.2	0.05	48	>99	99.7
2-furanyl	0.01	96	37	94.7	0.01	96	>99	97.7
2-furanyl					0.005	144	63	96.2
m-MeC_6H_4	0.1	48	95	98.5	0.05	48	92	99.5
α-$C_{10}H_7$	0.05	48	55	85.6	0.05	48	65	98.5
p-NCC_6H_4	0.1	48	>99	92.9	0.05	48	98.4	97.9
m-BrC_6H_4	0.1	48	>99	97.4	0.05	48	98.3	97.6
p-BrC_6H_4	0.05	48	>99	98.0	0.05	48	>99	98.4
p-ClC_6H_4	0.05	48	>99	91.2	0.05	48	>99	99.1
p-$O_2NC_6H_4$	0.05	48	>99	97.3	0.05	24	>99	99.4

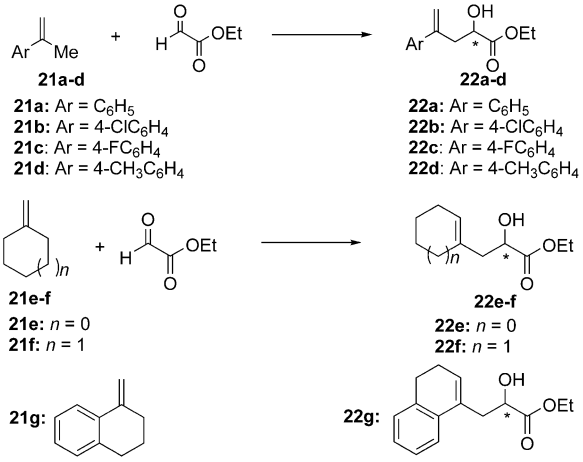
As a continuous effort for development of practical asymmetric catalysis of organic reactions, Ding and co-workers recently have successfully discovered two highly efficient and enantioselective catalysts for a quasi-solvent-free carbonyl ene reaction using the similar strategy mentioned above. The reaction of ethyl glyoxylate with a variety of olefins (**21**) could be carried out using 0.1–0.01 mol% of catalysts to give α-hydroxy esters (**22**) in good to excellent yields with up to 99% *ee*.[25] At the first stage of the screening, a ligand library containing ten diol ligands, including **20b–h**, **20j–k**, and (*R*)-3,3′-Me_2-BINOL, was employed for generation of titanium catalyst library with 55 members. After a quick screening, it was found that the modification of diol ligand at 6,6′-positions of BINOL with Br (**20g**) is quite effective for the enhancement of both the reactivity and the enantioselectivity of the reaction; this implies that an increase in Lewis acidity of titanium complexes might be a key point for achieving high efficiency and enantioselectivity in a carbonyl ene reaction. Accordingly, a second-generation library of chiral ligands with various electron-withdrawing groups (such as Br, I, CF_3) at the 6,6′-position of BINOL (Scheme 15) was set up. As expected, the catalyst library, generated by either homo- or heterocombination of chiral ligands shown in Scheme 15 with titanium isopropoxide, demonstrated excellent enantioselectivity (>94.9 ee) under nearly solvent-free conditions, even though the catalyst loading was reduced to 0.01 mol% (the solvent volume involved in the catalyst system was only ca. 1.3% of the whole system in these cases!). The catalysts formed by homocombination of **20n** or heterocombination of **20n** with **20o** with titanium isopropoxide were found to be superior to other combinations, affording α-hydroxy ester **22a** with 97.1% and 97.7% *ee*, respectively.



Scheme 15. A small (but focused) library of diol ligands for carbonyl ene reaction.

It was found that both **20n**/Ti/**20n** and **20n**/Ti/**20o** were highly efficient for the reactions of a variety of 2-arylpropenes (**21a–d**), including derivatives substituted with electron-withdrawing or electron-donating groups (Table 3). The olefin substrates could be also extended to cyclic system (**21e–f**), affording excellent enantioselectivities in the reactions of ethyl glyoxylate with methylenecyclopentane (**21e**) and methylenecyclohexane (**21f**), and the product **22e** was a key intermediate for the synthesis of a collagenase-selective inhibitor.[26] In the case of benzocyclic olefin substrate **22g**, the corresponding α-hydroxy esters **22g** could be obtained

Table 3. Enantioselective ene reactions between ethyl glyoxylate and representative olefins under nearly solvent-free conditions at 0 °C.



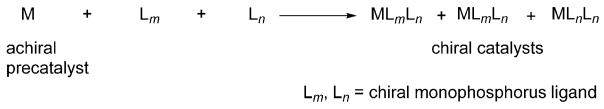
Olefin	Product	Catalyst (mol %)	Time [h]	Yield [%]	*ee* [%]
21a	(*R*)-**22a**	**20n**/Ti/**20n** (0.1)	48	98	98.2
21a	(*R*)-**22a**	**20n**/Ti/**20o** (0.1)	48	85	97.6
21a	(*R*)-**22a**	**20n**/Ti/**20n** (0.01)	72	76	97.2
21a	(*R*)-**22a**	**20n**/Ti/**20o** (0.01)	72	49	97.9
21b	(−)-**22b**	**20n**/Ti/**20n** (0.1)	48	89	99.4
21b	(−)-**22b**	**20n**/Ti/**20o** (0.1)	36	96	98.2
21c	(+)-**22c**	**20n**/Ti/**20n** (0.1)	48	83	98.4
21c	(+)-**22c**	**20n**/Ti/**20o** (0.1)	48	96	98.4
21d	(−)-**22d**	**20n**/Ti/**20n** (0.1)	36	92	97.1
21d	(−)-**22d**	**20n**/Ti/**20o** (0.1)	36	>99	97.0
21f	(*R*)-**22e**	**20n**/Ti/**20n** (0.1)	24	>99	91.6
21f	(*R*)-**22f**	**20n**/Ti/**20o** (0.01)	42	42	91.8
21g	(*R*)-**22g**	**20n**/Ti/**20n** (0.1)	48	97	92.2
21g	(*R*)-**22g**	**20n**/Ti/**20o** (0.1)	48	94	96.3

in 94–97 % yields with 92.6–96.3 % *ee*. The reaction of ethyl glyoxylate with α-methylstyrene could be also conducted on a 0.1 mol scale at 0 °C employing 0.05 mol % of **20n**/Ti/**20o** catalyst; the desired adduct **22a** was generated in >99 % yield and 95 % *ee*. To the best of our knowledge, this is the lowest catalyst loading in Lewis acid catalyzed asymmetric carbonyl ene reaction.[27]

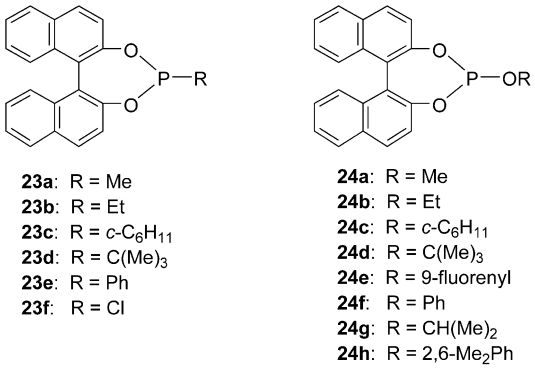
Reetz and co-workers recently reported the first use of mixture of chiral monodentate ligands to generate a transition-metal complex library for asymmetric hydrogenation.[28] The idea comes from recent significant achievement in asymmetric hydrogenation with chiral monophosphorus ligands. Many examples for homocombinations [$M(L)_2$] using 2:1 molar ratio of chiral ligand and metallic ion are known.[29] However, in the cases of the use of two different chiral ligands (L_m, L_n), the mixture of all three catalysts may well lead to enhanced enantioselectivity provided ML_mL_n is more reactive and selective than either of the traditional catalysts ML_mL_m or ML_nL_n (Scheme 16).

A series of BINOL-based mudular monophosphonites **23a–f** and monophosphites **24a–h** (Scheme 17) were utilized as chiral ligands to creat a chiral Rh catalyst library for olefin hydrogenation. The Rh-catalyzed hydrogenation of the acetamidoacrylate (**25**) in dichloromethane was first taken as the test reaction. As shown in Table 4, significant improved enantioselectivities (entries 10–12) were indeed observed by using two different phosphonites, whereby one component bears a small substituent R at the phosphorus center ((*R*)-**23a**, R = Me) and the other is characterized by steric bulk ((*R*)-**23c**, R = *c*-C_6H_{11} and (*R*)-**23d**, R = $C(Me)_3$). Although heterocombinations of the phosphite series ligands ((*R*)-**24a–g**) did not afford improvement of enantioselectivity, the proper combination of phosphonites (*R*)-**23** and phosphites (*R*)-**24** could significantly enhance the enantioselectivities (Table 1, entries 13–16).

Subsequent examination of the heterocombination strategy on the hydrogenation of the *N*-acylenamine **27a** (Table 5) was also successful. Heterocombination (*R*)-**23a**/(*R*)-**23d** with Rh provided the significant improvement of enantioselectivity (96.1 % *ee* (*S*)) for the formation of chiral amine **28a** relative to the respective homocombinations (*R*)-**23a**/(*R*)-**23a** (75.6 % *ee* (*S*)) and (*R*)-**23d**/(*R*)-**23d** (13.2 % *ee* (*S*)). This particular catalyst system was also workable for the reaction of other substrates, such as **27b**,**c**, affording the corresponding chiral amines **28b**,**c** in 95 % *ee* (*S*) and 97 % *ee* (*S*), respectively.

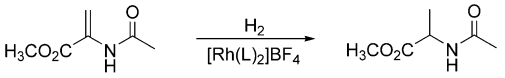


Scheme 16. Assembly of chiral catalysts using two different monodentate chiral ligands.



Scheme 17. Modular monophosphonite (**23**) and monophosphite ligands (**24**).

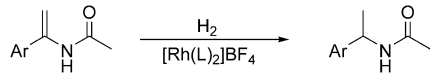
Table 4. Selected examples of Rh-catalyzed aysmmetric hydrogenation of **25**.



25 **26**

Entry	L_2	*ee* [%] (config.)
homocombinations		
1	(*R*)-**23a**/(*R*)-**23a**	91.8 (*S*)
2	(*R*)-**23b**/(*R*)-**23b**	94.4 (*S*)
3	(*R*)-**23c**/(*R*)-**23c**	92.0 (*S*)
4	(*R*)-**23d**/(*R*)-**23d**	93.3 (*S*)
5	(*S*)-**24a**/(*S*)-**24a**	76.6 (*R*)
6	(*S*)-**24b**/(*S*)-**24b**	83.6 (*R*)
7	(*R*)-**24c**/(*R*)-**24c**	94.6 (*S*)
8	(*S*)-**24d**/(*S*)-**24d**	95.4 (*R*)
9	(*S*)-**24e**/(*S*)-**24e**	92.4 (*R*)
heterocombinations		
10	(*R*)-**23a**/(*R*)-**23c**	97.9 (*S*)
11	(*R*)-**23a**/(*R*)-**23d**	97.8 (*S*)
12	(*R*)-**23c**/(*R*)-**23d**	94.1 (*S*)
13	(*R*)-**23c**/(*R*)-**24a**	96.4 (*S*)
14	(*R*)-**23d**/(*R*)-**24a**	98.0 (*S*)
15	(*R*)-**23c**/(*R*)-**24e**	95.6 (*S*)
16	(*R*)-**23d**/(*R*)-**24e**	97.2 (*S*)

Table 5. Rh-catalyzed hydrogenation of *N*-acyl enamines **27**.



27a Ar = Ph
27b Ar = 4-Cl
27c Ar = 2-naphthyl

28a Ar = Ph
28b Ar = 4-Cl
28c Ar = 2-naphthyl

Substrate	L_2	*ee* [%] (config.)
homocombinations		
27a	(*R*)-**23a**/(*R*)-**23a**	75.6 (*S*)
27a	(*R*)-**23d**/(*R*)-**23d**	13.2 (*S*)
27c	(*R*)-**23a**/(*R*)-**23a**	78.2 (*S*)
27c	(*R*)-**23d**/(*R*)-**23d**	$<$3.0 (*S*)
heterocombinations		
27a	(*R*)-**23a**/(*R*)-**23d**	96.1 (*S*)
27b	(*R*)-**23a**/(*R*)-**23d**	95.0 (*S*)
27c	(*R*)-**23a**/(*R*)-**23d**	97.0 (*S*)

Finally, the combinatorial search was also exemplified in the hydrogenation of dimethyl itaconate using phosphonites ligands (*R*)-**23**. Once again, the heterocombination (*R*)-**23a**/Rh/(*R*)-**23d** was the best catalyst system among various combinations, giving the corresponding product in 96.4% ee (*R*), while the homocombination of (*R*)-**23a**/Rh/(*R*)-**23a** and (*R*)-**23d**/Rh/(*R*)-**23d** gave lower *ee* values (90.2% and 57.3% respectively). It is noteworthy that the *ee* value remained nearly constant at quantitative conversion with reduced catalyst loadings (S/C = 6000, 95.8% ee; S/C = 20,000, 94.6% ee). Therefore, the heterocombination (*R*)-**23a**/Rh/(*R*)-**23d** can be considered as a promising catalyst system for practical hydrogenation of dimethyl itaconate.

In a more recent work, Reetz extended the combinatorial approach to the use of mixtures of chiral monodentate P ligands and achiral monodentate P ligands. The efficient chiral Rh-complex catalysts for asymmetric hydrogenation of acetamidoacrylate (**25**) were obtained and reversal of enantioselectivity was observed.[30a] After the disclosure of Reetz's research, Feringa reported the independent results for β-amino acids synthesis with a similar approach and observed improved conversion and enantioselectivity by heterocombination of monodentate phosphoramidite ligands.[30b] More recently, Feringa and co-workers have shown for the first time that the ligand combination approach is applicable for C–C bond formation. The chiral catalysts based on heterocombinations of monodentate phosphoramidite ligands are found to be more effective than the homocombinations.[30c]

Conclusion

We have attempted to show the principle and application of the combinatorial approach in the discovery of chiral catalysts for enantioselective reactions. The concept is focused on the creation of modular chiral catalyst libraries by using a two-component ligand-modification strategy on the basis of molecular recognition and assembly. The self-assembled chiral catalyst with two different ligands indeed exhibit a synergistic effect in terms of both enantioselectivity and activity in comparison with its corresponding homocombinations in some cases. Enantioselectivity and efficiency can be considered as two great challenges in asymmetric catalysis. The combinatorial approach has demonstrated its possibility in the discovery of highly efficient, enantioselective, and practical catalysts for enantioselective reactions. The other important point arises from this approach is that a question of "How much have we missed over the years by not using diversity-based approaches to catalyst discovery and optimization?" cannot be ignored any more. Accordingly, it makes sense to consider the use of mixtures of chiral ligands in asymmetric transition-metal catalysis, in spite of the fact that the systems of this kind contain at least three different catalysts or precatalysts. Therefore, this strategy has also provided an excellent opportunity for discovery of new "hits" from known chiral ligands.

Without question, an efficient asymmetric catalyst relies on the successful combination of a large number of interrelated variables, including rational design, intuition, persistence, and good fortune—not all of which are necessarily well understood, which renders this practice largely empirical.[2d] As a result, the possibility of using combinatorial chemistry methods in asymmetric catalysis research has been widely recognized to be highly desirable. Therefore, it can be expected more highly efficient and enantioselective catalysts, as well as unexpected classes of catalysts or catalytic reactions will be discovered in the future with the help of a combinatorial chemistry approach. We hope that the concept described in this paper will stimulate further research on the applications of a combinatorial approach in asymmetric catalysis.

Acknowledgement

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