Engineering Chiral Catalysts through Asymmetric Activation and Super High Throughput Screening (SHTS)

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A conceptually new strategy for asymmetric catalysis, namely *asymmetric activation*, in which a chiral activator selectively activates one enantiomer of a racemic chiral catalyst, and a highly efficient screening system for finding the most effective catalysts, namely *super high throughput screening* (SHTS), by which the reaction can be conducted in parallel and the *ee*% of the product is allowed to determine within minutes, are summarized in the present account. It is reasonable to believe that SHTS technique combined with asymmetric activation or deactivation principle will provide a very powerful methodology for finding the new catalysts and the best catalyst tuning for asymmetric reactions.

Keywords Chirality, asymmetric catalysis, asymmetric activation, asymmetric deactivation, high throughput screening

Introduction

Molecular chirality (handedness) is a principal element in nature that plays a key role in science and technology.[1] Among various approaches to achieve 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*[2] or *chirality amplification*[3] 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. 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).[1a] Therefore, development of highly efficient enantioselective catalysts is one of the most challenging endeavour 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 such enantioselective catalysts are metal complexes bearing chiral and non-racemic 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. In the present account, we will summarize our effort on the designing and screening of the highly efficient chiral catalysts for asymmetric reactions.

Results and discussion

Engineering the catalyst through asymmetric activation

Recently, a strategy whereby a racemic catalyst is

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selectively deactivated by a chiral molecule as a "chiral poison" has been reported to yield non-racemic products (Fig. 1a).[4] However, there should be an alternative, conceptually opposite strategy to asymmetric catalysts in which a chiral molecule (activator) selectively activates one enantiomer of a racemic chiral catalyst (Fig. 1b). The advantage of this asymmetric activation strategy over the deactivation counterpart is that the activated catalyst can produce a greater enantiomeric excess (x_{act}% *ee*) in the products than can the enantiomerically pure catalyst on its own (x% *ee*).

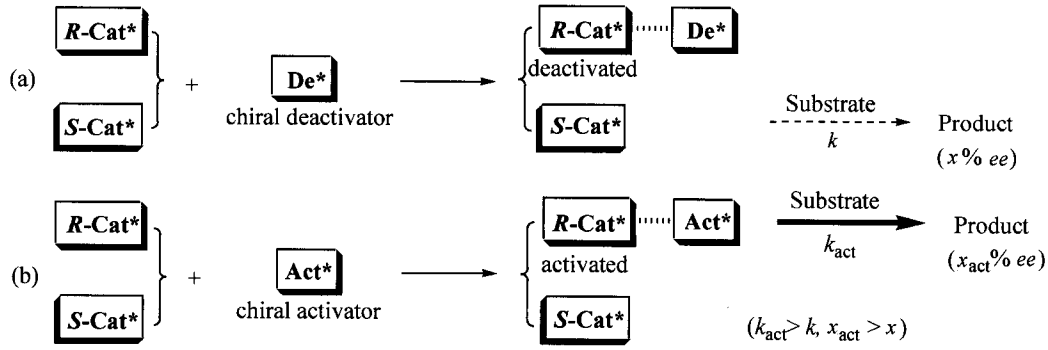
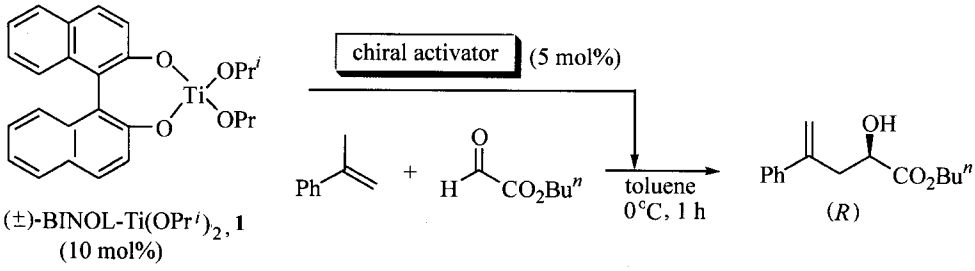


Fig. 1 Asymmetric deactivation (a) and asymmetric activation (b) of racemic catalyst.

One of the most successful examples for asymmetric activation of racemic catalysts should be BINOL-Ti complex catalyzed carbonyl-ene reaction.[5] Catalysis of the carbonyl-ene reaction[6] with glyoxylate by a racemic BINOL-Ti(OPr^i)$_2$ (**1**) achieves extremely high enantioselectivity by adding another diol for the enantiomer-selective activation. With 10 mol% of racemic (±)-BINOL-Ti(OPr^i)$_2$ complex and a half-molar amount (5 mol%) of (*R*)-BINOL activator, a remarkably high enantioselectivity of product (89.8% *ee*) was achieved (Table 1).

Table 1 Enantiomer selective activation of racemic BINOL-Ti(OPr^i)$_2$ (**1**)

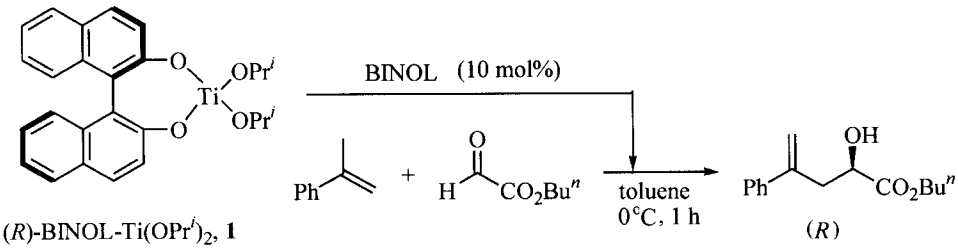


Run	Chiral activator	Yield (%)	*ee* (%)
1	none	5.9	0
2	2,2′-biphenol	20	0
3	(R)-5,5′-dichloro-4,4′,6,6′-tetramethyl-1,1′-bi-2-phenol	38	80.8
4	(R)-BINOL	52	89.8
5	(R)-BINOL (2.5 mol%)	35	80.0

Alternatively, the enantiopure (*R*)-BINOL-Ti(OPr^i)$_2$ (**1**) catalyst (10 mol%) is also activated by further addition of enantiopure (*R*)-BINOL (10 mol%) or even of racemic BINOL (10 mol%) to afford the product in higher chemical yields (82.1% and 69.2%, respectively) and enantioselectivity (96.8% *ee* and 95.7% *ee*, respectively) than those without additional BINOL (19.8% yield and 94.5% *ee*) (Table 2). Ki-

netics studies disclosed that the reaction catalyzed by the (*R*)-BINOL-Ti(OPr^i)$_2$/(*R*)-BINOL complex (**1'**) was 25.6 times as fast as that catalyzed by the (*R*)-BINOL-Ti(OPr^i)$_2$ (**1**) and the reaction catalyzed by the (*R*)-BINOL-Ti(OPr^i)$_2$/(*R*)-BINOL complex (**1'**) was 9.2 times as fast as that catalyzed by the (*R*)-BINOL-Ti(OPr^i)$_2$/(*S*)-BINOL (Fig. 2).

Table 2 Asymmetric activation of enantio-pure (*R*)-BINOL-Ti(OPr^i)$_2$ (**1**)



Run	BINOL	Yield (%)	*ee* (%)
1	None	19.8	94.5
2	(*S*)-BINOL	48.0	86.0
3	(*R*)-BINOL	82.1	96.8
4	(±)-BINOL	69.2	95.7

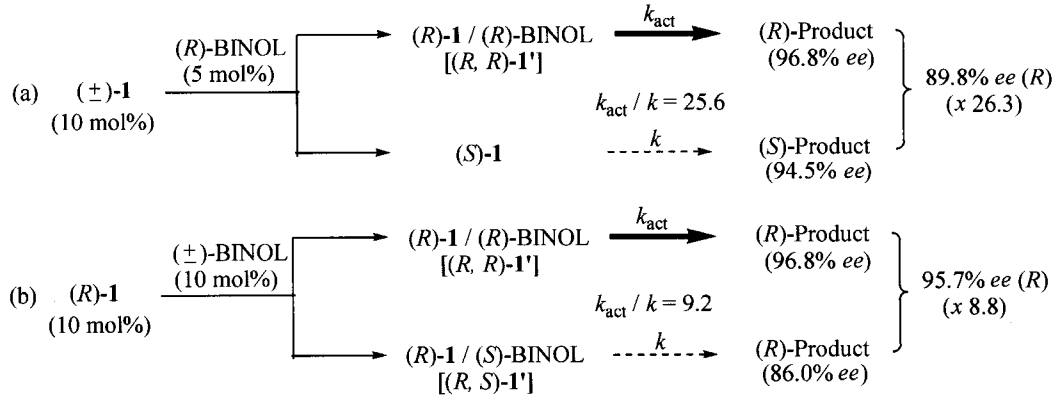


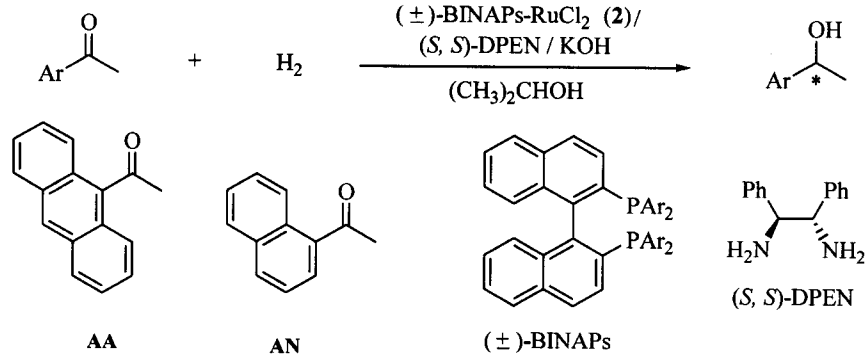
Fig. 2 Kinetic features of asymmetric activation of BINOL-Ti(OPr^i)$_2$.

A similar phenomenon of enantiomer-selective activation has been also observed in aldol,[7] hetero Diels-Alder[8] and Friedel-Crafts[9] reactions catalyzed not only by racemic but also an enantiomerically pure BINOL-Ti(OPr^i)$_2$ catalyst. The achiral additives, such as phenol, pentafluorophenol or 2-naphthol, were also found to significantly activate the (*R*)-BINOL-Ti(OPr^i)$_2$ catalyst for aldol reaction.[10] The same effect of additional equivalent activator was also found in BINOL-Zr complex catalyzed alkylation of aldehydes.[11]

Recently, Noyori *et al.* reported a remarkable example of enantioselective hydrogenation of simple prochiral ketones by the enantiopure BINAPs-RuCl$_2$(dmf)$_n$ complex **2** together with an enantiopure diamine and KOH.[12] For example, with the combinatorial use of (*S*)-BINAPs-RuCl$_2$/(*S*, *S*)-DPEN ((*S*, *S*)-1, 2-diphenylethylenediamine) as the catalyst, various ketones could be reduced under mild conditions in excellent yields and enantioselectivity. The dramatic effect of chiral 1,2-diamine on the efficiency and the enantioselectivity of the reaction provides an opportunity for investigating an asymmetric activation of racemic BINAPs-RuCl$_2$ catalysts for enantioselective catalysis of the carbonyl hydrogenation. A collaboration work reported by Mikami and Noyori envisions that a chiral diamine, such as (*S*, *S*)-DPEN, leads to a non-racemic hydrogenation prod-

uct, supporting the importance of chirality in the primary diamine activator for selective activation of one enantiomer of the (±)-BINAPs-$RuCl_2$ catalyst.[13] With a combined use of (±)-BINAPs-$RuCl_2$ and (*S*, *S*)-DPEN as the catalyst, the reaction product could be obtained in up to 90% *ee* and 95% yield (Table 3). The reduction of α, β-unsaturated cycloketone with coordinatively saturated (±)-BINAPs-$RuCl_2$/(*S*, *S*)-DPEN/KOH provides 95% *ee* of the product in quantitative yield.

Table 3 Asymmetric activation of racemic BINAPs-$RuCl_2$ catalyst **2** by enantio-pure DPEN[a]



a: Ar = 4-methylphenyl (TolBINAP)
b: Ar = 3,5-dimethylphenyl (DM-BINAP)
c: Ar = phenyl (BINAP)

Run	2	Ketone	Temp. (℃)	Time (h)	Yield (%)	*ee* (%)
1[b]	(*R*)-**2a**	**AA**	28	18	2	29 (*S*)
2[b]	(±)-**2a**	**AA**	28	18	< 1	0
3	(±)-**2a**	**AA**	28	18	28	80 (*R*)
4	(±)-**2a**	**AA**	80	10	99	80 (*R*)
5	(*R*)-**2a**	**AA**	80	10	99	81 (*R*)
6	(*R*)-**2a**	**AA**	80	10	91	40 (*R*)
7	(±)-**2b**	**AN**	28	4	99	81 (*R*)
8	(±)-**2b**	**AN**	− 35	7	95	81 (*R*)
9c	(±)-**2b**	**AN**	− 35	7	90	81 (*R*)
10	(*S*)-**2b**	**AN**	28	4	99	> 99 (*R*)
11	(*S*)-**2b**	**AN**	28	4	199	56 (*S*)

[a] Under H_2 (8 atm) atmosphere. Ketone:**2**:(*S*, *S*)-DPEN:NaOH = 250:1:1:2. [b] In the absence of (*S*, *S*)-DPEN.
[c] 0.5 Molar amount of (*S*, *S*)-DPEN per (±)-**2b** was used. **AN**:**2b**:**DPEN**:KOH = 250:1:0.5:2.

However, in this strategy *asymmetric activation* was established by non-preferential complexation of (±)-BINAP-$RuCl_2$ complex with enantiopure diamine based on the turnover frequencies (catalytic activities) between the diastereomers, which are critically dependent on the substrates.[14] The shortage of this protocol has been overcome by an *asymmetric activation/deactivation* strategy which achieve higher enantioselectivity *regardless of the substrate* by maximizing the difference in the catalytic activity between the catalyst enantiomers. The principle of this strategy is represented in Fig. 3.[14]

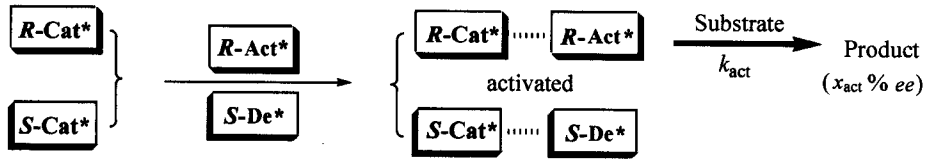
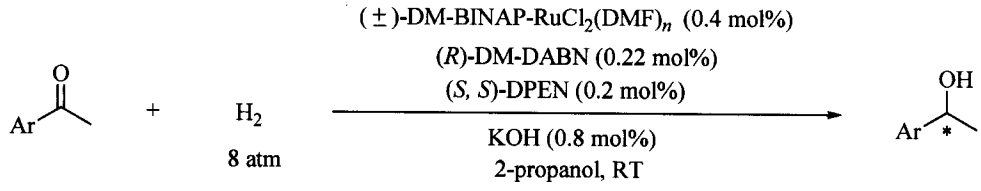


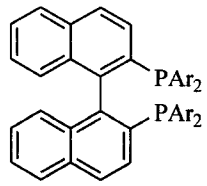
Fig. 3 Asymetric activation/deactivation strategy through preferential complexation.

The preferential complexation of (*S*)-BINAP-$RuCl_2$ with (*S*)-3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl (DM-DABN) was highly predictable by a modeling study and the structure was confirmed by single-crystal X-ray analysis.[14] The addition of a racemic DM-BINAP-$RuCl_2$ species to half equivalent of (*R*)-DM-DABN resulted in preferential complexation into the single diastereomeric (*R*)-DM-BINAP-$RuCl_2$/(*R*)-DM-DABN complex. The remaining (*S*)-DM-BINAP-$RuCl_2$ enantiomer gave a different complex with the sequential addition of enantiopure (*S*, *S*)-DPEN. The two dichloro complexes with DM-DABN and DPEN may be further converted into mono- or di-hydrido Ru species under hydrogenation conditions, while the DM-DABN complex is far less catalytically active under such conditions. The advantages of this strategy were demonstrated in enantioselective carbonyl hydrogenation. The resultant (*R*)-DM-BINAP-$RuCl_2$/(*R*)-DM-DABN and (*S*)-DM-BINAP-$RuCl_2$/(*S*, *S*)-DPEN complexes give better results than (±)-BINAP-$RuCl_2$/(*S*, *S*)-DPEN mixture in terms of both the enantioselectivity of the products and the scope of the ketonic substrates (Table 4). Thus the present *asymmetric activation/deactivation* protocol can be regarded as a paradigm shift in racemic catalysis by maximizing the difference in catalytic activity between enantiomeric catalysts.[14]

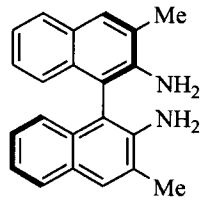
A further advanced strategy for asymmetric activation can be seen in the use of conformationally flexible ligands (Fig. 4) that achieve higher enantioselectivity than that attained by racemic ligands. As described above, combination of a racemic BINAPs-$RuCl_2$ with an equimolar amount of an enantiomerically pure diamine gives a 1∶1 mixture of two diastereomeric BINAPs-$RuCl_2$/(*S*, *S*)-DPEN complexes. When the chirality rigid BINAPs is replaced by a pro-atropisomeric BIPHEPs, the diastereomeric complexes are formed, in principle, in unequal amount. If the major diastereomer shows higher chiral efficiency than does the minor isomer, this strategy becomes more advantageous than the use of structurally similar BINAP analogues. In fact, a 3∶1

Table 4 Hydrogenation of ketones by the racemic DM-BINAP-$RuCl_2$ through asymmetric activation/deactivation

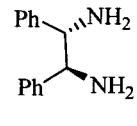




(±)-DM-BINAP
Ar = 3,5-dimethylphenyl



(*R*)-DM-DABN

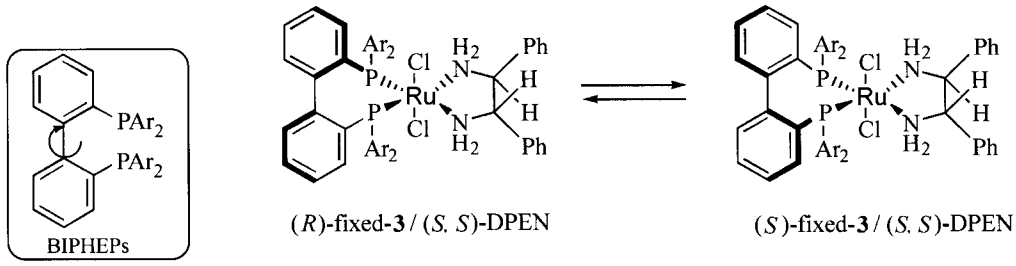


(*S*, *S*)-DPEN

Entry	Ar	*ee* (%)[a]
1	1-naphthyl	**96** (*R*), 80 (*R*)
2	2-naphthyl	**91** (*R*), 45 (*R*)
3	phenyl	**95** (*R*), 70 (*R*)
4	2-tolyl	**95** (*R*), 82 (*R*)
5	3-tolyl	**95** (*R*), 60 (*R*)
6	4-tolyl	**93** (*R*), 60 (*R*)

[a] The *ee* values printed in normal type were obtained without the presence of (*R*)-DM-DABN. The yields for all the reactions were over 99%.

mixture of the *S*/*S*, *S* and *R*/*S*, *S* diastereomers could be formed in 3 h at room temperature. The enantioselectivity by the DM-BIPHEP-$RuCl_2$/(*S*, *S*)-DPEN was higher than that by the (±)-DM-BINAPs-$RuCl_2$/(*S*, *S*)-DPEN complex at the same low temperature and high pressure. Thus, (*R*)-1-(1-naphthyl) ethanol was obtained with 92% *ee* in quantitative yield (Table 5).[15]



b: Ar=3,5-dimethylphenyl (DM-BIPHEP)
c: phenyl (BIPHEP)

$$\frac{(R)\text{-fixed-}\mathbf{3b}\,/\,(S,\,S)\text{-DPEN}}{(S)\text{-fixed-}\mathbf{3b}\,/\,(S,\,S)\text{-DPEN}} = 1:3$$

Fig. 4 Stereomutation of BIPHEPs-$RuCl_2$/DPEN complexes.

Table 5 Pro-atropisomeric BIPHEP ligand for enantioselective hydrogenation[a]

Run	Ketone	2 or 3	H_2 (atm)	Temp. (℃)	Time (h)	Yield (%)	*ee* (%)
1	**AN**	**3b**	8	28	4	>99	84
2[b]	**AN**	(±)-**3b**	8	28	4	>99	80
3	**AN**	**3b**	40	−35	12	>99	92
4[b]	**AN**	(±)-**2b**	40	−35	7	>99	89
5	**AN**	**3c**	8	80	10	>99	70
6[b]	**AA**	(±)-**2c**	8	80	10	>99	78

[a] BIPHEPs-$RuCl_2$ (**3**)/(*S*, *S*)-DPEN in 2-propanol was preheated at 80℃ for 30 min. Ketone:**3** or **2**:(*S*, *S*)-DPEN:KOH = 250:1:1:2. [b] Without pre-heating operation.

Speeding the catalyst optimization with super high-throughput screening (SHTS)

Combinatorial chemistry has been well-recognized as a useful strategy for the discovery and optimization of bioactive drugs, novel coordination complexes and solid-state materials.[16] Between the available split-and-mix and parallel strategies, the latter is more employable for lead optimization, where in the high throughput screening (HTS) is an essential technique for tuning a variety of modifications. A limited number of investigation has so far been reported on catalyst optimization for asymmetric reactions.[17] Using chiral HPLC or GC analysis of the enantiopurity of the product takes tediously long time and the chiral column is usually expensive, which forms a potential bottleneck in any combinatorial discovery effort. The application of circular dichroism (CD)-based detection system in HPLC on non-chiral stationary phases allows the simultaneous monitoring of the CD signal ($\Delta\varepsilon$), the UV absorption (ε) and their ratio ($g = \Delta\varepsilon/\varepsilon$) which is termed as dissymmetry factor. The g factor is independent of concentration and is linearly related to *ee* value.[18a] With this technique, the *ee*% of the product could be determined within minutes without separating the enantiomeric products in pure form. Therefore, combined application of combinatorial chemistry (CC) factory and HPLC-CD provides a highly efficient screening system which we refer to as *super high throughput screening* system for finding the most effective catalyst.[18b]

The success of this methodology has been exemplified by screening of chiral ligands and activators for enantioselective addition of diethylzinc to aldehydes on the basis of *asymmetric activation* concept. 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 could result in an activation of overall catalyst system.[19] As shown in Fig. 5, for activation of the diol-zinc catalyst system, the addition of a chiral nitrogen ligand is the most effi-

cient because of its ability to coordinate so strongly to the zinc cation.[20] Futhermore, bimolecular combination of activators with the diol-zinc complexes could conveniently achieve much larger extent of variety and steric tuning in catalysts.

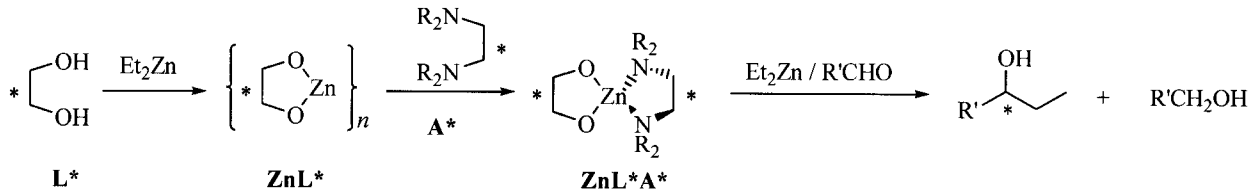


Fig. 5 Asymmetric activation of diol-zinc catalysts by nitrogen ligands.

We initially examined the primary library of chiral ligands (**L1***—**L5***) and chiral activators (**A1***—**A5***) (Fig. 6), for which the lead catalyst could be further optimized for the next generation of the chiral ligands and activators. The activation effect was actually observed in terms of both reactivity and enantioselectivity of the reaction. For example, **L2*** and **A4*** promoted the reaction to give (*S*)-1-phenylpropanol with 8.2% *ee* (54% yield) and 1.1% *ee* (64% yield), respectively. However, the combined use of **L2*** and **A4*** quantitatively provided the product with 37.4% *ee* (*S*). The best combinations from the primary combinatorial library were found to be **L5***/**A4*** and **L5***/**A5*** to provide (*S*)-1-phenylpropanol with up to 65% *ee* and in quantitative yields.

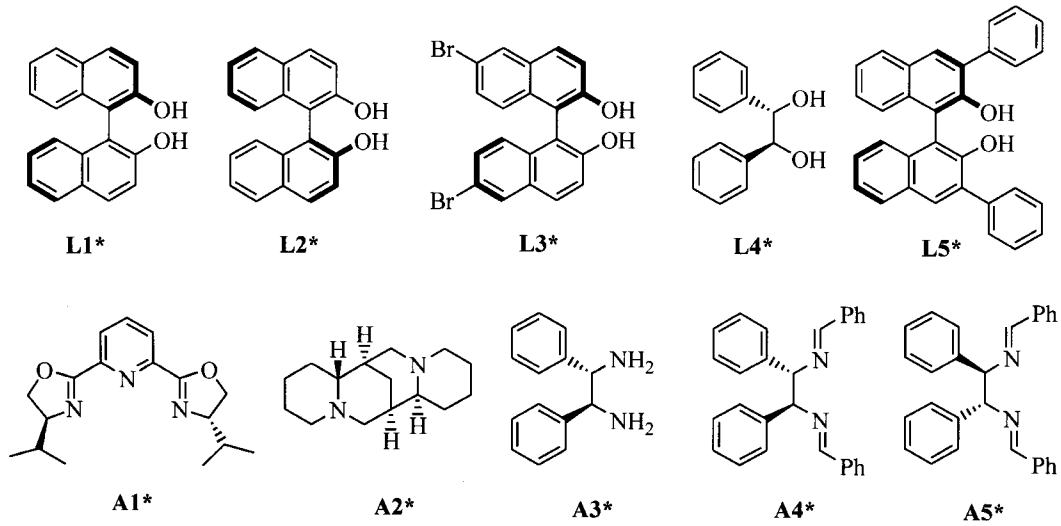
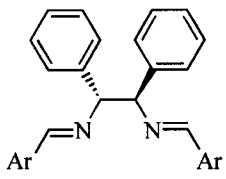


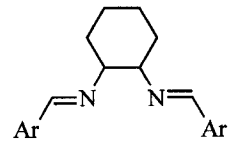
Fig. 6 Primary library ligands (**L1***—**L5***) and chiral activators (**A1***—**A5***).

On the basis of the results derived from primary combinatorial library, we then created a new library of diimine activators with 12 members (**A4***—**A15***) (Fig. 7). It was found that all library members significantly activate the Zn-**L5*** complex and produce 1-phenylpropanol in higher yields and with higher enantioselectivities than those obtained by only using the ligands or activators themselves. Particularly, the reaction could be completed within several minutes in the case of **L5***/**A9***, and thus provided the best results (100% yield, 90% *ee*).

The reaction catalyzed by the best combination **L5***/**A9***, was further optimized by lowering the reaction temperature to −78℃. It is great to find that (*S*)-1-phenylpropanol was obtained with 99% *ee* and in quantitative yield. Under the optimized conditions, **L5***/**A9***, is proven to be extremely effective for the addition of diethylzinc to a range of aldehydes (Table 6).[21]



	Ar
A4*: *S, S*	Ph
A5*: *R, R*	Ph
A6*: *S, S*	2,6-$Cl_2C_6H_3$
A7*: *R, R*	2,6-$Cl_2C_6H_3$
A8*: *S, S*	2,4,6-$Me_3C_6H_2$
A9*: *R, R*	2,4,6-$Me_3C_6H_2$



	Ar
A10*: *S, S*	Ph
A11*: *R, R*	Ph
A12*: *S, S*	2,6-$Cl_2C_6H_3$
A13*: *R, R*	2,6-$Cl_2C_6H_3$
A14*: *S, S*	2,4,6-$Me_3C_6H_2$
A15*: *R, R*	2,4,6-$Me_3C_6H_2$

Fig. 7 Secondary generation library of chiral activators.

Table 6 Asymmetric addition of Et_2Zn to aldehydes in the presence of **L5***/**A9*** to provide the secondary alcohols[a]

Entry	R	Yield (%)	*ee* (%)	Configuration
1	phenyl	100	99.0	*S*
2	phenyl[b]	100	97.0	*S*
3	*p*-methoxyphenyl	100	98.5	S
4	*m*-methoxyphenyl	100	96.4	n.d.
5	*p*-chlorophenyl	99	98.5	*S*
6	*p-tert*-butylphenyl	100	99.0	n.d.
7	β-naphthyl	100	93.8	*S*
8	α-naphthyl	93	91.5	*S*

[a] 10 mol% of **L5*** and **A9*** were used. [b] Only 2 mol% of **L5*** and **A9*** were used.

"Positive non-linear effect" [(+)-NLE][3] or "asymmetric amplification" is a very attractive phenomenon in catalytic asymmetric processes, since it gives enantioselectivities which are improved with respect to expectations based on the *ee* values of the auxiliary. Therefore, because of asymmetric amplification, high-enantiopurity chiral ligands need not necessarily be applied to achieve high enantiopurities of product. Nevertheless one has to make a partial resolution of chiral ligands from their racemic forms.

In the enantioselective addition of diethylzinc to aldehyde, the asymmetric amplification is well recognized to be a consequence of an *in situ* increase in the *ee* value of the active catalyst, since racemic ligand is trapped in the more stable, unreactive *meso* species.[22] In principle, if racemic ligands are used alone, the reaction will definitely give racemic product. The addition of an alternative nonracemic additive (which should be cheap and easily obtainable) to the racemic catalyst may enantioselectively generate a new species of dinuclear zinc complex with one enantiomer of racemic ligand through "non-self-recognition" to release the opposite enantiomer of catalyst for asymmetric catalysis (Fig. 8). To exemplify this strategy, Oguni *et al.*'s racemic amino alcohols[22a] were chosen to carry out asymmetric catalysis by adding nonracemic additives.

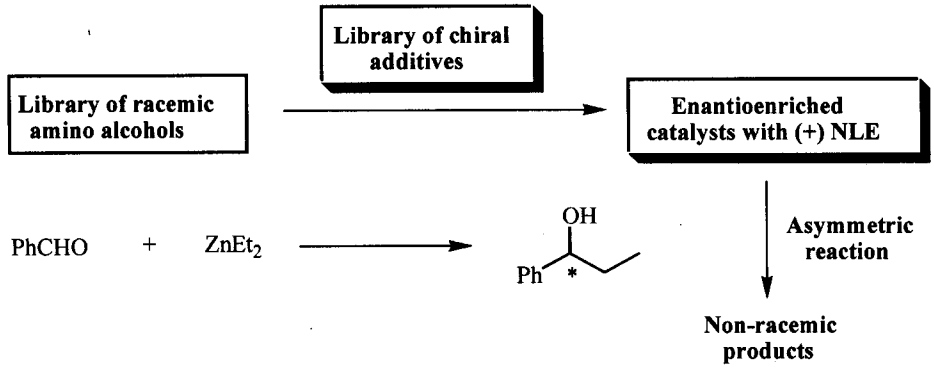


Fig. 8 Asymmetric catalysis with racemic amino alcohols in the presence of nonracemic additives.

Investigation on the effect of various random chiral additives, such as amino acids, tartaric acid, diols, diamine, diimine, and simple amino alcohols, was carried out on the enantioselectivity of ethylation of benzaldehyde with diethylzinc catalyzed by racemic DB1.[23] The influences of chiral additives were really observed on the asymmertic induction of reaction. For example, (*R*)-BINOL catalyzed the reaction to give *R* product (8.2% *ee*), but the addition of (*R*)-BINOL to the reaction system catalyzed by racemic DB1 resulted in the formation of *S* product (8.5% *ee*). Similarly, the reaction promoted by (*S*)-2-*N*, *N*-dimethylamino-2′-hydroxy-1, 1′-binaphthyl (DM-NOBIN) yielded *S* product (89% *ee*) and the addition of (*S*)-DM-NOBIN to the racemic DB1 system gave *R* product (38% *ee*). These data could be interpreted by a phenomenon where a catalytically inert heterochiral dimeric zinc complex may be formed between the chiral additive and one of the enantiomers of racemic amino alcohol through non-self-recognition; as a result the zinc complex of racemic amino alcohol is enantioselectively enriched and catalyzes the reaction to give nonracemic product. From the primary random screening, we found that amino alcohol was one type of effective chiral additive candidates for this purpose.

The *super high throughput screening* strategy again proved to be a powerful technique for finding such chiral additives. With the lead mentioned above, a library of optically active amino alcohols (**AA1—AA13**, Fig. 9) was then created by parallel synthesis from amino acids, and a family of racemic amino alcohols (**DB1—DB5**), which have been reported to show significant asymmetric amplification,[22a] were also formed. The combined use of 10 mol% of racemic amino alcohols (**DB1—DB5**) and half an equivalent amount (5 mol%) of optically active additives in the presence of diethylzinc afforded a chiral catalyst library of 65 members, which were then evaluated with *super high throughput screening* techniques. Fig. 10 shows the details of the screening results. It is obvious that the chiral additives with large steric hindrance at the hydroxy-functionalized carbon, (**AA8—AA13**), were more influential on the enantioselectivity of the reaction than the simple amino alcohols, **AA1—AA7**. Particularly, **AA10**, **AA12** and **AA13** showed significant synergetic effect on the enantioselectivity of the reaction. For example, with only **AA13** (5 mol %) as chiral inducer, (*R*)-1-phenylpropanol was obtained in 15.6% *ee*. However, the addition of racemic **DB1** or **DB2** (10 mol %) to **AA13**-catalyzed reaction system resulted in the formation of *S* product in 65.8% and 70.4% *ee*, respectively.

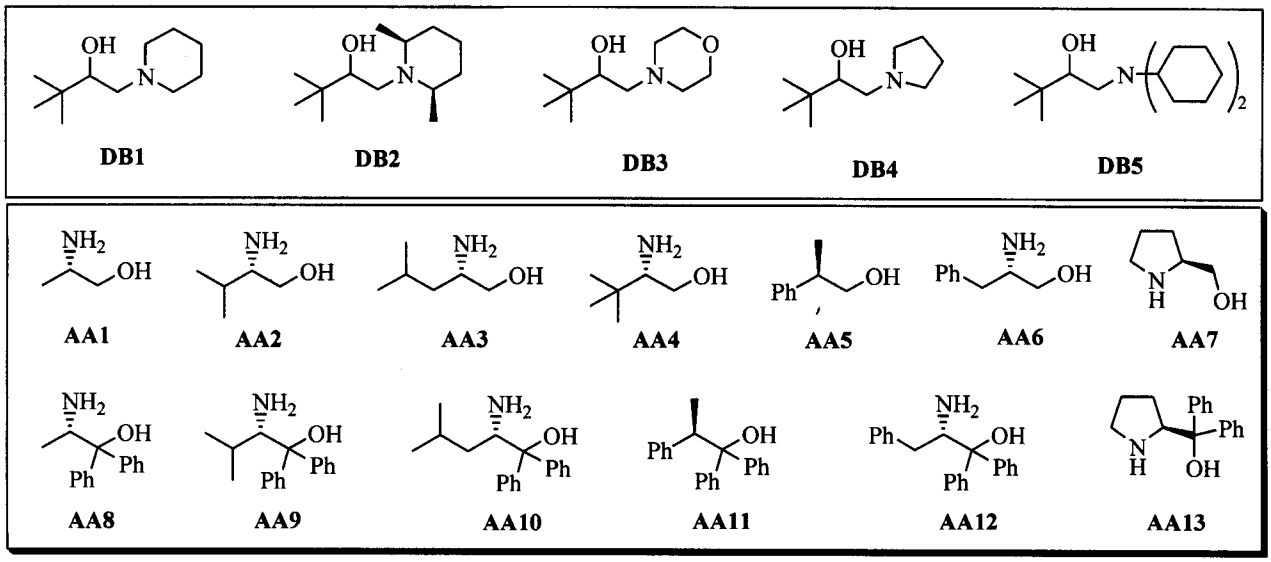


Fig. 9 Racemic (**DB**) and nonracemic (**AA**) ligands employed for creating the chiral catalyst library.

The reactions catalyzed by the better combinations, **AA12/DB1**, **AA12/DB2**, **AA13/DB1**, and **AA13/DB2**, were further optimized in paralell by varying the molar ratio of racemic **DB** to chiral **AA** and decreasing

the reaction temperature to −20℃ and −40℃. (*S*)-1-Phenylpropanol can be obtained with up to 92.7% *ee* and in >95% yield under the catalysis of **AA13/DB2** (ratio: 1/2; 5 mol% of **AA13**) at −40℃. Catalyst combinations **AA12/DB1**, **AA12/DB2**, **AA13/DB1** and **AA13/DB2** also proved to be effective for the ethylation of a variety of aldehydes under the optimized conditions (Table 7).

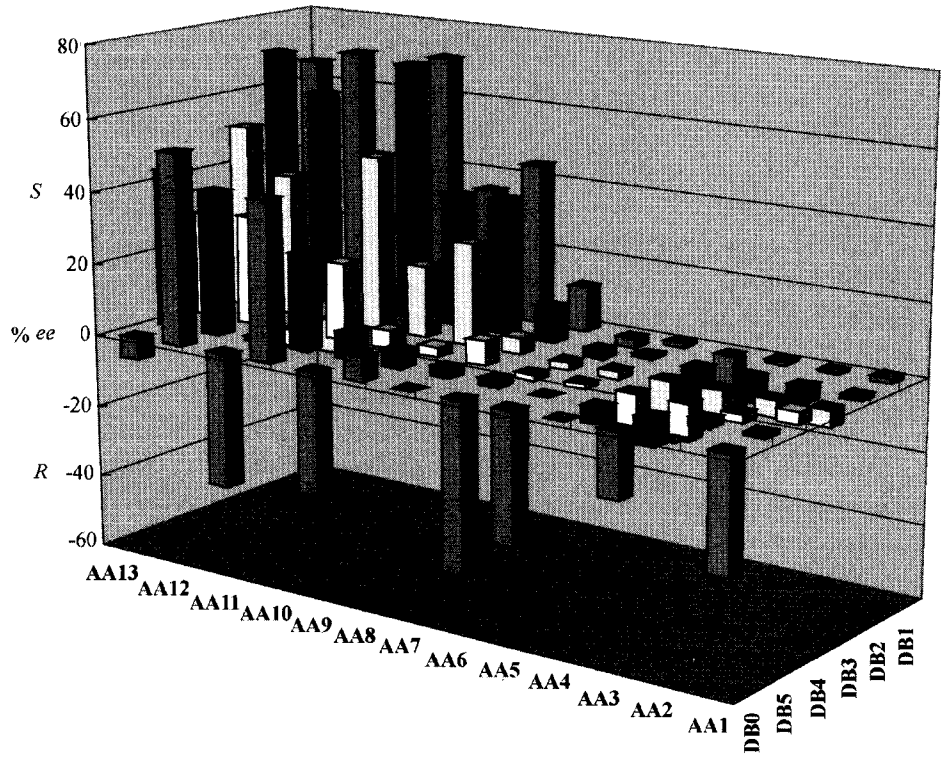
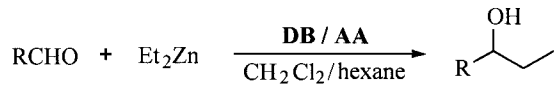


Fig. 10 Screening of combinations of chiral additives (**AA1**—**AA13**) and racemic amino alcohols (**DB1**—**DB5**) for enantioselective addition of diethylzinc to benzaldehyde.

Table 7 Enantioselectivities for the ethylation of aldehydes with the catalysis by racemic **DB** in the presence of optically active **AA**:[a] parallel screening of matched substrate/catalyst pairs



Entry	R	AA12/DB1	AA12/DB2	AA13/DB1	AA13/DB2
1	phenyl	86.0	86.1	**92.7**	90.6
2	*p*-chlorophenyl	69.9	82.3	84.6	**92.1**
3	*m*-tolyl	85.7	81.0	**90.1**	87.3
4	*p*-anisyl	87.5	90.3	90.0	**91.4**
5	*trans*-styryl	67.7	**82.3**	69.4	69.4
6	*o*-anisyl	69.8	76.7	74.5	86.3
7	ferrocenyl	81.9	90.6	**91.7**	72.9
8	*p*-dimethylamino-phenyl	23.6	55.6	36.2	**81.0**[b]
9	α-naphthyl	69.9	72.2	69.3	**86.3**
10	*p*-tolyl	74.7	80.0	**82.4**	80.0
11	*m*-anisyl	79.2	**80.7**	76.9	76.4

Continued

Entry	R	AA12/DB1	AA12/DB2	AA13/DB1	AA13/DB2
12	*p*-bromophenyl	76.6	73.6	**82.7**	79.5
13[c]	*trans*-propenyl	78.3	**84.4**	80.7	**84.4**

[a] All of the reactions were carried out under −40℃ unless otherwise noted in CH_2Cl_2-hexane mixed solvent for 48 h with the catalysis of racemic **DB1** (10 mol %) and optically active **AA** (5 mol %). The conversions of the aldehydes were > 90%. All the *ee* values were determined by HPLC or GC on chiral columns. [b] The reaction was carried out at 0℃. [c] The reaction was carried out at −20℃.

The nonlinear effect in the present catalytic system was disclosed by an investigation of the influence of the molar ratios between **AA13** and (*R*)-**DB1** and (*S*)-**DB1** on the enantioselectivity of the reaction (Fig. 11). The different behavior of the nonlinear effects in the **AA13**/(*R*)-**DB1** and **AA13**/(*S*)-**DB1** system again supported the presence of non-self-recongition between **AA13** and **DB** and also indicated the differences in their non-self interactions.[23]

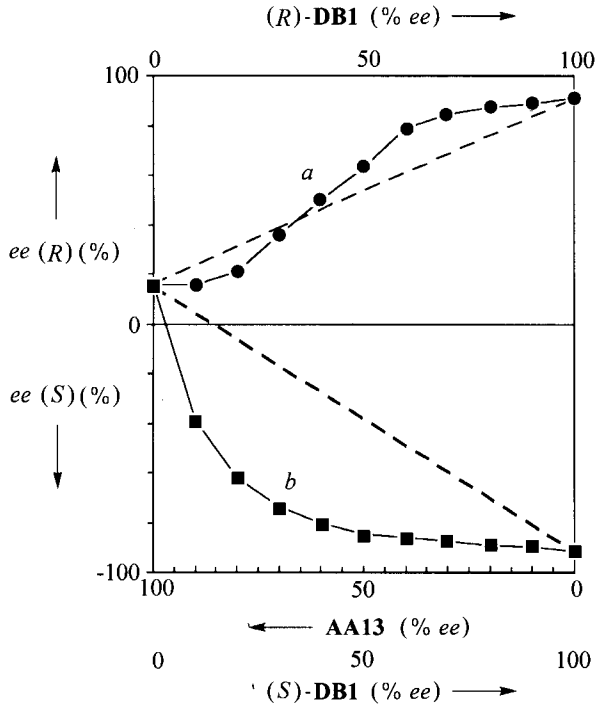


Fig. 11 Enantioselectivity of the reaction of benzaldehyde with diethylzinc catalyzed by mixing **AA13** with (*R*)-**DB1** (a) and (*S*)-**DB1** (b). The broken lines indicate the expected values when the reactivity difference between **AA13** and (*R*)-**DB1** or (*S*)-**DB1** is not considered.

Future perspective

Asymmetric activation will provide a general effective strategy for asymmetric catalysis involving racemic or conformationally flexible ligands without tedious optical resolution. Not only chiral organic molecules but also chiral metal complexes can be used as chiral activators through hetero-multimetallic activation.[24] Asymmetric activation will be further developed as a new chiral doping techniue in smectic phase of racemic liquid crystalline molecule.[25] *Asymmetric activation* concept may be also extended to the solid-state process.[26,27] Kagan stated that in asymmetric catalysis, one must no more ignore the modern methods of combinatorial chemistry and fast screening.[28] We believe that our *super high throughput screening* (SHTS) technique combined with *asymmetric activation* principle will provide a very powerful methodology for finding the new catalysts and best catalyst tuning for asymmetric reactions.

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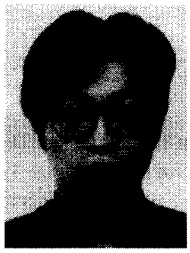

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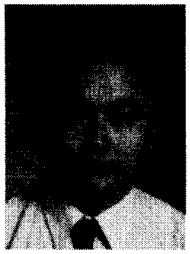

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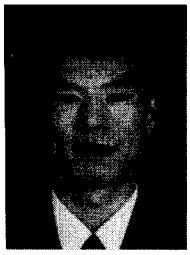

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