Multicatalyst System in Asymmetric Catalysis

JIAN ZHOU

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MULTICATALYST
SYSTEM IN
ASYMMETRIC
CATALYSIS
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MULTICATALYST SYSTEM IN ASYMMETRIC CATALYSIS

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The past 50 years have witnessed vast achievements in asymmetric catalysis, which has reached to such a level that excellent enantioselectivity for many reactions can now be finally achieved, given intensive screenings and necessary substrate modification. On the other hand, if existing catalytic asymmetric protocols are under scrutiny by the criterion of the ideal synthesis, most of them have ample room for further improvement in terms of atom utilization, energy consumption, and waste generation. For example, the modification of substrates with an activating group or bulky shielding group is a widely adopted strategy to achieve the desired reactivity and stereoselectivities, but such a manipulation unfortunately decreases the synthetic efficiency, if the introduced auxiliary is essentially unnecessary for the final optically active products. Therefore, a long-standing challenge confronting chemists in the field of asymmetric catalysis is to meet the guidelines of ideal synthesis, namely to struggle for ideal asymmetric catalysis. Undoubtedly, chiral catalysts play a crucial role in turning this goal into reality, and the exploitation of new catalyst systems is indispensable for improving the efficiency of known protocols, and for realizing asymmetric transformations currently unattainable. However, the discovery of new powerful chiral catalysts is by no means a piece of cake, as evidenced by the fact that although enormous efforts have been devoted in the past 50 years, only a handful of privileged chiral catalysts are available that are capable of realizing excellent stereoselectivities in more than 10 kinds of reactions. In addition, there in no way exists a single privileged chiral catalyst that can solve all the problems. Accordingly, to achieve ideal asymmetric catalysis not only requires the development of new privileged chiral catalysts, but also demands strategies to make the best of known enantioselective catalysts.
The multicatalyst system catalysis, on the basis of the combination of multiple distinct catalysts with at least a chiral one, has recently emerged as a promising strategy to tackle the challenges in achieving ideal asymmetric catalysis. As the victory of battles builds on the coordination of all the soldiers, no matter ordinary or supersoldiers with capabilities beyond normal limits, so does the remarkable efficiency of the multicatalyst system originate from the cooperation of distinct multiple catalysts, no matter chiral or achiral. The “two heads are better than one” effect, realized by a multicatalyst system, can be classified into three major types: (1) asymmetric cooperative catalysis (simultaneous activation of distinct reaction partners); (2) asymmetric double activation catalysis (double activation of one substrate); and (3) asymmetric assisted catalysis (the generation of an enhanced catalytic species via catalyst interaction). By any of the three activation models, the energy barrier of the reaction is lowered down to a more effective extent than by monocatalysis. In addition, multicatalyst systems are in particular attractive for the development of tandem reactions, which essentially mimic the multienzymatic system that Nature employs in the complex molecule synthesis.

In 2010, I was invited to write a focus review on the recent advances in multicatalyst promoted asymmetric tandem reactions (Chem. Asian J. 2010, 5, 422–434), which witnessed the rapid development of this area in the past several years. Intrigued by this topic, Dr. Jonathan T. Rose, the senior editor of Wiley-VCH, encouraged me to develop this topic into a book. Because of our research interest in this field, I regarded this as a golden opportunity to get an in-depth understanding of this emerging area, and spent 3 years collecting and assorting literatures, while preparing the draft. During the process, it came to my attention that although this area has received much attention nowadays, there is indeed thirst for a book to provide a comprehensive definition, discussion, and summarization about the application of multicatalyst system in asymmetric catalysis, as all the known review articles just focused on one aspect of this research field. For example, the use of a certain additive to greatly improve the reactivity and stereoselectivity of an asymmetric reaction is well-documented, but there is no proposed standard to distinguish the additive-enhanced catalysis from multicatalyst system catalysis. In addition, almost all the known review articles focus on introducing asymmetric cooperative activation realized by multicatalyst system, and pay little attention to the other two important types, asymmetric double activation catalysis and assisted catalysis. Therefore, based on my 15 years’ experience in the field of asymmetric catalysis, I leave no stone unturned to give a thorough introduction about the function, classification, and application of multicatalyst systems in asymmetric catalysis, and special attention is paid to differentiate multicatalyst system catalysis from multifunctional catalysis or additive-enhanced catalysis. Accordingly, unless to show the basic concepts, only literature reports with sufficient control experiments to demonstrate the crucial role of each catalyst component of the multicatalyst system are selected and introduced.

This book begins with discussion on the criterions of ideal asymmetric catalysis and the challenges on the way to this lofty goal, and proposes the development of new activation models and new chiral catalysts as a promising strategy to achieve ideal asymmetric catalysis. The following chapter introduces the known models of
activation in both nucleophiles and electrophiles, summarizes the early examples of multcatalyst promoted asymmetric reaction, discusses the basic activation models provided by multcatalyst system, presents the differences between multcatalyst system catalysis and multifunctional catalysis, proposes a standard to distinguish multcatalyst system catalysis from additive-enhanced asymmetric catalysis, and finally, highlights some representative additive-enhanced asymmetric reactions, which might be helpful for readers to compare and strengthen their understanding.

The following chapters are organized into interlinked sections and will benefit readers to grasp the advantages of multcatalyst catalysis, which include: asymmetric multifunctional catalysis (Chapter 3); asymmetric cooperative catalysis (Chapter 4); asymmetric double activation catalysis (Chapter 5); asymmetric assisted catalysis (Chapter 6); asymmetric catalysis facilitated by photochemical or electrochemical method (Chapter 7); multcatalyst system realized asymmetric tandem reaction (Chapter 8); waste-mediated reactions (Chapter 9); and multcatalyst system mediated asymmetric reactions in total synthesis (Chapter 10).

This book is timely and reflects the latest achievement in this area till 2013, which would be helpful for players in this field to have a quick overview and to design new related chemistry. Importantly, it provides wonderful opportunities for readers outside this field to be aware of this important emerging area and attract more students and chemists to engage in this research field. Moreover, the knowledge and information will also provide an educational opportunity for the public to learn that asymmetric catalysis can be done in “greener” ways to make useful enantioenriched substances, as well as to change their perceptions of organic synthesis as a dangerous, toxic, hazardous, and pollutive science.

I would like to avail myself of this opportunity to thank the Wiley-VCH editorial staff, in particular to Jonathan T. Rose for proposing and encouraging me to write this book, and to Amanda Amanullah, Ho Kin Yunn and Shalini Sharma who are of precious help for the development of this project. I also thank my students Yu-Hui Wang, Miao Ding, Yu-Lei Zhao, Xiao-Ping Yin and Fu-Ming Liao for their kind help in proofreading.
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1

TOWARD IDEAL ASYMMETRIC CATALYSIS

JIAN ZHOU AND JIN-SHENG YU

1.1 INTRODUCTION

The past 50 years have witnessed tremendous achievements in the field of asymmetric catalysis, with its importance being widely recognized by the society, as evidenced by the 2001 Nobel Prize in Chemistry awarded to Sharpless, Knowles, and Noyori for their contribution to chiral metal catalysis [1]. Today, chiral products have found many applications in many areas of daily life, from perfumes, food additives to drugs and many others. As one of the most promising methods to produce chiral products, it is no exaggeration to say that better the asymmetric catalysis, better the human beings’ lives. Apart from the vast demands for chiral products from the pharmaceutical industry, other applications such as agricultural chemicals, flavors, fragrances, chiral polymers, and liquid crystals constitute the ever-increasing demands. In particular, two-thirds of prescription drugs are chiral, and the majority of new chiral drugs are single enantiomers [2]. On the one hand, the demands for optically active compounds, often as single enantiomers, stimulate intensive researches to invent efficient synthetic methods; on the other hand, the gradually easier access of chiral compounds escalates their applications in more aspects of modern life, which in turn motivates the further development of efficient and economic asymmetric synthesis.

Since Nozaki and Noyori reported the first asymmetric reaction using a chiral copper complex as the catalyst in 1966 [3], new concepts and new chiral metal catalysts have been continuously created and applied to various unprecedented enantioselective reactions, which greatly facilitate the synthesis of optically active compounds. The asymmetric synthesis is further greatly fueled by the rediscovery of asymmetric...
organocatalysis as we enter the new millennium [4]. Currently, metal catalysis, biocatalysis, and organocatalysis are the three pillars that asymmetric catalysis is built upon. By these well-established and complementary tools, it becomes increasingly convenient to achieve a useful level of enantioselectivity (>90% ee) for the synthesis of given chiral products, given careful combination of a suitable chiral catalyst and reaction parameters.

Along with the triumph over the accomplishments, some may argue that the field of asymmetric catalysis is in its twilight, as the basic concepts and outlines have been established, which results in opinions that the development of catalytic asymmetric reactions is no longer challenging and intriguing, because excellent enantioselectivity for a specific reaction could be finally achieved as long as intensive screenings of reaction parameters are conducted. This could not be farther from the truth, if existing catalytic asymmetric protocols are under scrutiny by the criterion of the ideal synthesis [5]: a product must be “prepared from readily available, inexpensive starting materials in one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in quantitative yield.” In 2009, the Nobel laureate, professor R. Noyori further emphasizes that [6], to synthesize our future, synthetic chemists should “aim at synthesizing target compounds with a 100% yield and 100% selectivity and avoid the production of waste. The process must be economical, safe, resource efficient, energy efficient and environmentally benign. In this regard, the atom economy [7] and the E-factor [8] should be taken into account.”

Although such lofty goals might never be realized, the ambition and basic ideas outlined in these principles show the right but formidable way that chemists in the field of asymmetric catalysis should take to further their researches, considering the immense obligations of chemists to tack a range of existing or predicted social and global issues associated with environment, ecology, energy, resources, and health [9].

Not surprisingly, if evaluated strictly by the standards of “ideal synthesis,” most catalytic enantioselective protocols developed to date have great potential to be improved, presumably because the past and current attention is primarily paid to how to ensure excellent selectivity and reasonable yield. Generally, the development of a highly enantioselective asymmetric catalytic reaction involves three important procedures:

1. **Catalyst Screening and Evolution.** The purpose of this step is to identify a promising chiral catalyst. Usually, intensive screening of chiral catalysts that could be readily available is conducted at this step. If lucky enough, the ideal chiral catalyst which could achieve excellent stereoselectivity comes out soon. Otherwise, the modification of the optimal chiral catalysts to improve the selectivity is necessary, which is unfortunately unavoidable in most studies.

2. **Substrate Modification.** The manipulation plays an important role in reaction development, especially when initial screenings fail to afford a promising chiral catalyst capable of achieving excellent stereoselectivity. The purpose of this procedure is to modify the substrates with a suitable auxiliary group to interplay with the chiral catalyst, to maximize the reactivity and stereoselectivity of a given reaction. The decoration of substrates could be conducted from two
INTRODUCTION

3. Optimization of Reaction Parameters. A lot of factors, including temperature, solvent, and additive, remarkably influence the reactivity and stereoselectivity of catalytic asymmetric reactions. The influences are so great that the reversal of stereoselectivity happens in some extreme cases, by altering the reaction solvent, temperature, or additive, even if the chiral catalyst remains the same. Accordingly, careful optimization of reaction parameters is a routine procedure for the establishment of a suitable reaction condition to obtain excellent yield and selectivity. In most cases, better enantioselectivity is obtained by running the reaction at low temperature, which leads to prolonged reaction time and aggravates the consumption of energy. The use of aqueous solution or non-toxic organic solvent is favorable, but toxic solvents such as benzene and polyhalogenated solvents have to be used in many cases, for the sake of excellent ee values. Additives are versatile to improve the reactivity and selectivity, although their role remains to be investigated.

Obviously, these procedures mainly focus on how to improve stereoselectivity, and pay little attention on atom utilization, energy consumption, and E-factor for the synthesis of a given chiral product. Of course, it is not that chemists in the field of asymmetric catalysis do not care about the guidelines of “ideal synthesis,” but they are in a dilemma as to pursue excellent enantioselectivity or to achieve low E-factor.

A good example to elucidate the aforementioned dilemma is the catalytic asymmetric Strecker synthesis of α-aminonitriles [10], which are versatile precursors of α-amino acids and diamines. This reaction, discovered by Adolph Strecker in 1850 [11], comprises a one-pot three component condensation of an aldehyde 1 with ammonium chloride and KCN (Scheme 1.1). Driven by the vast demand of various non-natural optically active α-amino acids, the corresponding catalytic asymmetric synthesis has been intensively studied, but the use of amine protecting groups to realize excellent enantioselectivity and yield is indispensable for all available protocols. Since the pioneering work of the Lipton group in 1996 [12], various types of N-protected preformed imines 4 have been tried, allowing highly enantioselective synthesis of a broad scope of N-protected α-aminonitriles 2. In terms of atom economy and enantioselectivity, these protocols are unambiguously successful (100% atom economy and >90% ee for the Strecker reaction step). While the N-protecting groups of the thus obtained α-aminonitriles are useless for further transformation,
TOWARD IDEAL ASYMMETRIC CATALYSIS

1) The Strecker reaction

\[
\begin{align*}
\text{R} - \text{H} & \quad \xrightarrow{\text{NH}_4\text{Cl, KCN}} \quad \text{R} - \text{CN} \\
\text{NH}_2 & \quad \xrightarrow{\text{hydrolysis}} \quad \text{NH}_2 - \text{COOH}
\end{align*}
\]

2) Catalytic asymmetric variants using different N-protected aldimes

\[
\begin{align*}
\text{NH}_2 & \quad \xrightarrow{\text{asymmetric catalysis}} \quad \text{NH}_2 - \text{COOH} \\
\text{Ph} & \quad \xrightarrow{\text{hydrolysis}} \quad \text{deprotection}
\end{align*}
\]

Note: numbers in parenthesis refer to the molecular weight of Pg of imines.

3) To be realized

Protecting-group-free cyanation of imines

\[
\begin{align*}
\text{R} - \text{H} & \quad \xrightarrow{\text{asymmetric catalysis}} \quad \text{NH}_2 - \text{CN} \\
\text{NH}_2 & \quad \xrightarrow{\text{Protecting-group-free}} \quad \text{Excellent enantioselectivity} \\
\text{Excellent yield}
\end{align*}
\]

One-pot protecting-group-free Strecker reaction

\[
\begin{align*}
\text{R} - \text{H} & \quad \xrightarrow{\text{asymmetric catalysis}} \quad \text{NH}_2 - \text{CN} \\
\text{NH}_2 & \quad \xrightarrow{\text{Excellent yield}} \quad \text{Excellent selectivity}
\end{align*}
\]

SCHEME 1.1 A discussion about the atom utilization of Strecker reaction.

ye must be removed and will no longer be present in the desired α-amino acids, if the unprotected α-amino acids are the desired products. As a consequence, the use of N-protecting groups, either to improve the enantiofacial control or to enhance the reactivity, inevitably decreases the atom utilization of the Strecker synthesis of unprotected amino acids. It should also be noted that the molecular weight (MW) of the discarded auxiliary is much higher than the desired product in some extreme cases. For example, in the synthesis of phenylglycine, the molecular weight of several types of protecting groups is higher than that of phenylglycine (151). In addition, the removal of the protecting group entails at least one more step, which will incur yield loss and the generation of more waste, and leads to high E-factor.

Ideally, the development of catalytic asymmetric protecting-group-free [13] Strecker reactions using unprotected imines 5 or a one-pot three component version from aldehydes 1, ammonia and HCN would allow a “perfect” synthesis of unprotected chiral α-amino acids, which is consonant with the criterion of “ideal
synthesis.” This research is highly rewarding but very challenging. Hopefully, it will turn into reality, with the development of asymmetric catalysis, new concepts, and new chiral catalysts.

Another convincing example to demonstrate the big gap between the current stage of asymmetric catalysis and “practical elegance,” is the catalytic enantioselective synthesis of methyl dihydrojasmonate \( \text{6} \) \cite{14}. Today, it has become a phenomenon in fine perfumery since its debut in “Eau Sauvage” (Dior, 1966), and it is difficult to find a formula without it (Figure 1.1).

The intrinsic olfactive values of four stereoisomers of Hedione have been determined: the \( \text{cis} \)-isomers of \( \text{6} \) are much more powerful (about 70 times) than the \( \text{trans} \), and the \( (+-\text{cis}-\text{6}) \) proved to be the only stereoisomer that has an odor. Even the \( (-\text{-cis}-\text{6}) \) is very weak, and more earthy than floral in smell. Acid- or base-induced epimerization at C(2) of the \( \text{cis} \)-isomers is rapid, and the \( \text{trans} \) isomers are thermodynamically favored by a ratio of 95:5 at room temperature. Although the use of Hedione as equilibrium mixtures is popular, one can achieve a striking “radiance” of the perfume when using \( (+-\text{cis}-\text{6}) \), which is used under controlled \( 5 < \text{pH} < 7 \) or stabilized conditions to avoid equilibration. Accordingly, catalytic asymmetric synthesis of \( (+-\text{cis}-\text{6}) \) becomes interesting to industry. However, although almost 50 years have passed, there is still no satisfactory catalytic asymmetric method for such a highly profit-making process, which might be very surprising for most researchers in the field of asymmetric catalysis.

The catalytic asymmetric hydrogenation of didehydrohedione \( \text{7a} \) is a straightforward method for the synthesis of \( (+-\text{cis}-\text{methyl dihydrojasmonate 6}) \), but the asymmetric hydrogenation of such a tetrasubstituted olefin proves to be difficult (Scheme 1.2). After intensive studies, Rautenstrauch and Genêt found that the use of 2.9 mol% of a Me-DuPhos \( \text{8a/Ru} \) complex could catalyze the hydrogenation in a scale of 1.0 kg, to afford \( (+-\text{cis}-\text{6}) \) in 92% yield with 70% ee \cite{15}. Although this protocol might be enough for profit, there is much room for further improvement such as (i) raising the ee values and (ii) decreasing the catalyst loading. This is also a convincing example to demonstrate the ineffectiveness of the substrate-modification procedure. Although higher ee values might be reasonably anticipated if varying the methyl ester to a bulky one will result in, such a manipulation has no practical use, as it will greatly raise the cost, and most undesirably, the common ester exchange methods will lead to epimerization.

\textbf{FIGURE 1.1} Methyl dihydrojasmonate \( \text{6} \) and its presence in some brands of perfumes.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Methyl dihydrojasmonate \( \text{6} \) and its presence in some brands of perfumes.}
\end{figure}
1) Industrialized asymmetric hydrogenation

\[ \text{7a (1 kg)} \] \[ \text{8a (2.9 mol\%)} \] \[ \text{H}_2 (35 \text{ bar}), \text{CH}_2\text{Cl}_2, 24 \text{ h} \] \[ \text{(+)-cis-6} \] \[ (92\%, \text{cis/trans} = 98/2, 70\% \text{ ee}) \]

2) An alternative route

\[ \text{7b} \] \[ \text{9} \] \[ \text{1. NaH} \] \[ \text{2. TMSCl} \] \[ \text{SCEM} \] \[ \text{NMP NaCl} \] \[ \text{8b (98% ee)} \] \[ \text{Excellant diastereoselectivity} \] \[ \text{Excellent enantioselectivity} \] \[ \text{Excellent yield} \]

3) Is it possible?

\[ \text{7b} \] \[ \text{CH}_2\text{CO}_2\text{Me} \] \[ \text{Asymmetric catalysis} \] \[ \text{syn-selective Michael addition} \] \[ \text{(+)-cis-6} \]

**SCHEME 1.2** Catalytic asymmetric synthesis of (+)-cis-methyl dihydrojasmonate 6.

An alternative route involving the chirality transfer by rearrangement reactions is developed by Fehr [16]. Although the starting 2-pentylcyclopent-2-en-1-ol 9 is easily available and 98% ee is achieved for the desired (+)-cis-6, this method involves longer steps and the use of much more reagents, which inevitably produces more waste.

The direct synthesis of (+)-cis-6 via the Michael addition of methyl acetate to enone 7b is probably the most economical route, but seemingly impossible. As can be expected, thermodynamically stable trans-diastereomer is favored. However, it is worthwhile to explore the unprecedented highly enantioselective synthesis of cis-diastereomer through Michael addition using \( \alpha \)-substituted enones. If workable, this approach is greener and more economical than the hydrogenation of didehydrohedione 7a, which is synthesized from bromination/HBr elimination of trans-6. Interestingly, Krause and Ebert have observed that the conjugate addition of diallylcuprate to enone 7b could afford the corresponding cis-product in 85:15 dr if a diastereoselective protonation of the intermediate enolate is taken [17]. This result might be helpful for the development of the envisioned Michael addition.

The above two pertinent examples clearly demonstrate the current status and the challenges confronting asymmetric catalysis, together with the direction which synthetic chemists in this field should go. We are at most halfway through to ideal asymmetric catalysis, although substantial achievements have been made to enable...
the facile synthesis of chiral products in excellent enantioselectivity. As the bar continues to be raised on the synthesis of chiral compounds in a more efficient and environmentally benign way, enantioselectivity is no longer the sole criterion to evaluate the success of asymmetric reactions, and atom- and step economy must be taken into consideration. The fact that the absolute amounts of waste generated in the production of the high-value chiral products are lower than those in the bulk chemicals industry should not be viewed as an excuse not to pursue greener asymmetric catalysis. On the contrary, one must take the pressure as an opportunity for invention of new concepts, new chiral catalysts, and new methodologies.

1.2 CHALLENGES TO REALIZE IDEAL ASYMMETRIC CATALYSIS

When it comes to defining the “success” of a given catalytic asymmetric reaction, the enantiomeric excess and the yield of the desired product are the two crucial factors that are mostly emphasized nowadays, if not solely. In addition, the catalyst loading is also regarded as being important, but it is a flexible standard, as the cost on chiral catalyst for a reaction depends on both the price and loading of the chiral catalyst employed.

Despite question and debate, it will be gradually adopted to evaluate a given catalytic asymmetric reaction by both the conventional standard (enantioselectivity and yield) and the more challenging criterion (atom efficiency and E-factor). Accordingly, the criterions for ideal asymmetric catalysis, summarized from literature wisdom [18], refer to the highly stereoselective synthesis of desired chiral products from cheap starting materials in excellent yield by simple operation, in the presence of simple and easily available chiral catalyst with high turnover frequency (TOF), with most of the atoms of the products being brought into full play, either by emerging into the final products or by benefiting the following synthesis. To achieve such a goal, the following challenges are to be overcome.

1) Develop catalytic asymmetric synthesis with high atom utilization  
In other words, high atom utilization means the preparation of desired enantioenriched products from simple and easily available starting materials. As mentioned above, a common strategy to improve the reactivity and selectivity of a given reaction is to modify the substrates with a suitable auxiliary, which functions as an activating group to improve the reactivity or as a shielding group to benefit the enantiofacial control. By this strategy, excellent yield and selectivity could be relatively easily obtained for given asymmetric reactions; however, the introduction and removal of the auxiliary group decreased the atom efficiency of the whole process to obtain the desired optically active compounds, as shown in Figure 1.2.

On the other hand, the atom utilization of the corresponding process would be substantially improved for an auxiliary-free process, but it is a daunting task to develop the corresponding catalytic asymmetric reaction. Two major challenges should be tackled: one is to realize reasonable reactivity, and the other is to secure excellent enantiofacial control. In many cases, simple substrates are less reactive than those
1) Activating or shielding group enabled asymmetric catalytic reactions

![Diagram 1](attachment:image1)

2) Activating or shielding group-free asymmetric catalytic reactions

![Diagram 2](attachment:image2)

**FIGURE 1.2** Toward high atom utilization catalytic asymmetric synthesis.

with an activating group, or difficult to realize excellent enantiofacial control if lacking a bulky shielding groups to render enough enantiofacial discrimination. This was exemplified by the Michael addition of 3-prochiral oxindoles to nitroolefins, recently developed by Barbas III and coworkers (Scheme 1.3) [19]. In the presence of a bifunctional tertiary amine-thiourea catalyst $12a$, the $N$-Boc protected 3-methyl oxindole $10a$ readily reacted with the nitroethylene $11a$ to give the desired product $13a$ in 65% yield and 96% ee. This reaction is of high synthetic value, and has been applied to the total synthesis of ($-\$)-esermethole; however, the use of $N$-Boc protected 3-methyl oxindole is indispensable for reaction development, as the corresponding $N$-methyl analogue $14a$ is reluctant to work with nitroethylene under the same reaction condition. The high reactivity of the $N$-Boc protected 3-prochiral oxindoles is possibly due to the electron-withdrawing effect of the Boc group, which enhanced the acidity of the methine proton, thereby allowing the deprotonative activation to be more facile [20]. Although the $N$-Boc could be regarded as a masked $N$-methyl group of ($-\$)-esermethole, the use of $N$-methyl 3-methyl oxindole $14a$ as the starting material would be more atom efficient. First, not only the Boc protecting group has a bigger molecular weight than methyl group (101 vs. 15), and the excessive atoms will not emerge into the final natural product ($-\$)-esermethole, but also it takes three steps to prepare $N$-Boc protected 3-methyloxindole $10a$ from 4-methoxyisatin $15a$ via Grignard addition/Boc protection/hydrogenation, with the sacrifice of one more equivalent of (Boc)$_2$O [21]. In contrast, $N$-methyl 3-methyloxindole $14a$ could be prepared easily from the corresponding indole derivative $16a$ [22]. Second, an extra step to reduce the Boc group by using LiAlH$_4$ is needed for the synthesis of ($-\$)-esermethole, which decreased the step economy of the whole process.

Similar to the aforementioned reactions, many known catalytic asymmetric reactions are based on reactive substrates such as trimethylsilyl-based nucleophiles and activated methylene (or methine) compounds. In sharp contrast, the direct utilization of unactivated simple reagents such as ethyl acetate and acetonitrile for reaction
design still remains largely unexplored and constitute a big challenge for organic chemists. To enable the simple, cheap but easily available substrates to join the field of asymmetric catalysis, the development of new activation models and new powerful enantioselective catalysts is the only feasible way, which is challenging, exciting but highly rewarding.

2) Improve catalyst efficiency for asymmetric catalysis  The chiral catalyst plays a central role in the development of asymmetric reactions, the properties and cost of which largely determine the efficiency and practicability of the corresponding process. Ideally, the catalyst efficiency for an asymmetric reaction refers to the use of a simple and cheap, easy to handle chiral catalyst, with low toxicity and high tolerance to impurities, to achieve the required enantiomeric excess for the synthesis of the desired product in high turnover number (TON) and TOF, under a mild reaction condition.

To improve the catalyst efficiency, it is necessary to develop a suitable method to estimate it. In 2009, Todd and Richards proposed a formula, Asymmetric Catalyst
TOWARD IDEAL ASYMMETRIC CATALYSIS

Efficiency (ACE) [23], to quantitatively evaluate the small molecule chiral catalysts, which emphasize that a chiral catalyst is more efficient if fewer atoms are employed to deliver the required enantiomeric excess for the product. By this concept, the ratio of the molecular weight of the product to that of the catalyst is used for the calculation of the catalyst effectiveness, which also takes into account the catalyst loading, the yield, and the ee values of the desired product. The definition of ACE is introduced in Scheme 1.4. The ACE is a straightforward descriptor for the evaluation of the catalyst efficiency of an asymmetric reaction, as evidenced by the calculated ACE values for some representative reactions. In accordance with their extensive industrial usage, the ACE values of the transition-metals-catalyzed asymmetric hydrogenation reactions are much higher than oxidation reaction and C–C bond forming reactions (entries 1–2 vs. 3–4). For example, an industrial multi-tonne synthesis of (S)-metolachlor via asymmetric hydrogenation of ketimines 21a [24] has an ACE value of 76,096. Remarkably, Noyori’s protocol of hydrogenation of acetophenone [25] has an ACE value of up to 206,858. On the other hand, the ACE value of the Sharpless oxidation of allyl alcohol [26] is 3.81, and that of the Hajos–Parrish–Eder–Sauer–Wiechert reaction [27] is 46.1.

Although the formula proposed by Todd and Richards might be further improved to be generally accepted for the evaluation of the catalyst efficiency, its basic idea is noteworthy. The efficiency of a catalytic asymmetric reaction should be evaluated not only by the enantioselectivity and yield of the product, but also by the amount and the price of catalyst employed and the relative size of the catalyst to the product.

Two important solutions for raising the catalyst efficiency of a given asymmetric reaction should be highlighted. First, the development of low catalyst loading reaction is very important. Even if the chiral catalyst is very expensive, the low catalyst loading could effectively decrease the expense for the synthesis of the optically active products. As shown by the two examples of transfer hydrogenations, although the chiral catalysts are very expensive (119.5 and 381.71 euros per gram, respectively), the costs on catalyst for the synthesis of 1.0 mmol of the desired product are low (0.00007 and 0.001 euros, respectively), because the catalyst loading of two reactions are extremely low. Second, the use of cheap and simple chiral catalyst for reaction design is of significant importance. Although both the epoxidation of alkene 24a and intramolecular aldol condensation of triketone 27 suffer from high catalyst loading, as compared with the hydrogenation reaction, the low cost of the chiral catalyst (0.21 and 0.76 euros per gram, respectively) still allows the synthesis of compounds 26a and 29 in low cost (entries 3 and 4).

It is worth mentioning that it is not suitable to evaluate the synthetic efficiency of a given reaction just by the ACE values, as is evidenced by the highly enantioselective biomimetic synthesis of α-amino esters from α-keto esters via chiral base-catalyzed transamination reaction using simple benzyl amines, recently developed by Shi and coworkers (Scheme 1.5) [28].

In the first generation, only α-keto esters with a bulky CEt3 ester group could be transaminated to the corresponding α-amino esters in excellent ee values, when using a simple chiral bifunctional catalyst 32a, with a molecular weight of 366.50. For example, product 33a was obtained in 70% yield with 92% ee, the corresponding
### General catalytic asymmetric reaction

\[
\text{ACE} = \frac{\text{MW}_P}{\text{MW}_{\text{cat}}} \times \frac{1}{\text{mol}\%} \times \frac{\text{ee}}{100} \times \text{yield}
\]

- **Relative size of catalyst and product**
- **Amount catalyst needed**
- **Quantity of excess of major enantiomer**

### Table 1.4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Representative Reaction</th>
<th>ACE</th>
<th>Cat. Cost [Eur] (a)</th>
<th>Cost of Product [Eur] (b)</th>
<th>TON (\text{h}^{-1})</th>
<th>ACES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="#" alt="Reaction 1" /></td>
<td>206,858</td>
<td>119.5</td>
<td>0.000,07</td>
<td>50,322</td>
<td>4310</td>
</tr>
<tr>
<td>2</td>
<td><img src="#" alt="Reaction 2" /></td>
<td>76,096</td>
<td>381.71</td>
<td>0.001</td>
<td>226,364</td>
<td>38,048</td>
</tr>
<tr>
<td>3</td>
<td><img src="#" alt="Reaction 3" /></td>
<td>3.81</td>
<td>0.21</td>
<td>0.012</td>
<td>17</td>
<td>7.62</td>
</tr>
<tr>
<td>4</td>
<td><img src="#" alt="Reaction 4" /></td>
<td>46.1</td>
<td>0.76</td>
<td>0.002,9</td>
<td>1.6</td>
<td>2.31</td>
</tr>
</tbody>
</table>

\(a\) The catalyst cost refers to the catalogue prices (2009) of 1 g of the less expensive enantiomer, if the two differ; 
\(b\) The cost of 1 mmol of the excess of the major enantiomer given by MW\(P\)/1000 * catalyst cost [1g]/ACE.

### Scheme 1.4

Definition of ACE and examples of some typical asymmetric reactions.

ACE value was 4.87. On the other hand, the improved protocol allowed the use of synthetically more favorable tert-butyl α-keto esters to be converted to the desired α-amino ester 33b in 87% yield with 94% ee, but the molecular weight of the bifunctional catalyst 34a was up to 694. If we judge the synthetic efficiency of the two generations of this reaction solely by ACE values, a misleading conclusion will
SCHEME 1.5 Evolution of chiral base-catalyzed transamination reaction.

come out, as the ACE value of the second generation is decreased to 2.77, due to the higher molecular weight of product 33a over 33b and the smaller molecular weight of catalyst 32a over 34a. However, the synthetic efficiency of the latter protocol is obviously better than the former in that the use of t-Bu ester allows the conversion of the product readily to the corresponding amino acid, and less atoms from the shielding group are wasted.

In addition to the ACE values, we regard the ideal catalyst for an asymmetric reaction should not contain precious elements due to their scarcity, which are in possible danger of becoming unavailable [29]. Another concern about the catalyst is that the use of heavy metal catalysts should be avoided due to its possible contamination of the products.

3) Develop operationally simple and environmentally benign protocols
Owing to the resource-intensive nature of catalytic asymmetric reactions, the following factors other than excellent atom utilization and catalyst efficiency should be taken into consideration to realize ideal asymmetric catalysis.

1. The substrate scope of the protocol should be broad, allowing the synthesis of desired products with significant structural diversity. This is very important for the structure–activity relationship studies, which contribute to the development of new biological probes and drugs.

2. The reaction medium should be environmentally benign, or the reaction is carried out in (quasi) solvent-free condition. The use of toxic solvents should
be avoided, and reactions in water are favorable. The use of supercritical carbon
dioxide or recyclable solvents such as ionic liquids and fluorocarbon oil to
develop catalytic asymmetric reactions should be encouraged.

3. High tolerance of the reaction to impurities, including air and moisture com-
patibility, is very important, which greatly simplifies the operation and ensures
the reproducibility of the reaction.

4. It is very important to achieve excellent stereoselectivity for given reactions
at room temperature. Running the reaction at low temperature is indeed an
effective method to benefit the enantiofacial control, but the reaction time
is greatly prolonged to days, which aggregates the energy consumption and
entails extra attention. If excellent stereoselectivity could be accomplished
when running the reaction at room temperature, not only the reaction time could
be shortened as compared with the corresponding low-temperature process,
but the reaction is free of constant temperature and low temperature baths and
special care, which is highly economical and convenient.

5. The work-up procedure should be easy and enable the removal of heavy metal
catalysts, and importantly, minimize waste production, including the contam-
inated water. This is a crucial factor to decrease E-factor of an asymmetric
process.

6. The reaction could be easily scaled up to allow the synthesis of optically
active products in sufficient quantity, a factor very important for the practical
application. Currently, many C–C bond forming reactions are limited to a
0.1 mmol or less, as the stereoselectivity of the reaction will be eroded if
the reaction scale is enlarged. The reasons why some catalytic asymmetric
reactions are difficult to be scaled up are complicated, but it is for sure a
challenge worthwhile to overcome.

In Table 1.1, 10 criterions for ideal catalytic asymmetric synthesis are listed,
which are summarized from the opinions of literature reports. These standards clearly
demonstrate that there is a big gap between the current status of asymmetric catalysis
and the ideal one, as most of the available protocols only meet two or three criterions.
How to realize the ideal catalytic asymmetric processes that meet most of the criterions
listed in this table is a formidable task for organic chemists in the future.

1.3 SOLUTIONS

The development of new activation models and new chiral catalysts plays a pivotal
role in tackling the challenges to achieve ideal asymmetric catalysis. During the
past 50 years, the discovery of new activation modes of substrates contributes to the
development of more powerful chiral catalysts, which in turn enables some asym-
metric transformations to be performed in a more efficient manner, and to be closer to
ideal asymmetric catalysis. In particular, the rediscovery of organocatalysis gives an
impetus to make some asymmetric reactions more efficient. Before this century, the
### TABLE 1.1 Detailed for Ideal Catalytic Asymmetric Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Criterions</th>
<th>Ideal Catalytic Asymmetric Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Enantioselectivity</td>
<td>Excellent (&gt;90%)</td>
</tr>
<tr>
<td>2</td>
<td>Yield</td>
<td>Excellent (&gt;90%)</td>
</tr>
<tr>
<td>3</td>
<td>Atom utilization</td>
<td>High (Most of the atoms of the products are incorporated into the final desired chiral products)</td>
</tr>
<tr>
<td>4</td>
<td>Catalyst efficiency</td>
<td>High ACE values&lt;br&gt;Avoid the use of precious elements&lt;br&gt;Low molecular weight catalyst&lt;br&gt;High TON and TOF</td>
</tr>
<tr>
<td>5</td>
<td>Substrate scope</td>
<td>Substantially broad, could achieve significant structural diversity</td>
</tr>
<tr>
<td>6</td>
<td>Reaction medium</td>
<td>Aqueous medium, toxicless solvent or recyclable reaction medium</td>
</tr>
<tr>
<td>7</td>
<td>Operation simplicity</td>
<td>With high air and moisture compatibility</td>
</tr>
<tr>
<td>8</td>
<td>Reaction temperature</td>
<td>Room temperature</td>
</tr>
<tr>
<td>9</td>
<td>Work-up and ecology</td>
<td>Low E-factor (Minimize waste generation, including contaminated water)</td>
</tr>
<tr>
<td>10</td>
<td>Scalability</td>
<td>Readily scale-up for application.</td>
</tr>
</tbody>
</table>

Asymmetric catalysis is dominated by chiral metal catalysis, although early examples of using an organic molecule to catalyze the enantioselective reaction are reported several decades ago [30]. In the late 1990s, small organocatalysts were demonstrated to be able to solve important problems in asymmetric synthesis, as evidenced by the use of chiral quaternary ammonium salt as a powerful phase-transfer catalyst for the highly enantioselective C-methylation of indanones by Merck scientists [31]; the use of chiral ketones to catalyze the asymmetric epoxidation of simple alkenes pioneered by the group of Yang [32], Shi [33], and Denmark [34], independently; the first application of H-bonding catalysis in asymmetric Strecker reactions by Jacobsen [35] and Corey [36], and their coworkers; and the use of minimal peptides for the enantioselective kinetic resolution of alcohols by Miller group [37]. These researches, together with the two landmark works in 2000 (one by List, Lerner, and Barbas on enamine catalysis; and the other by MacMillan on iminium catalysis), enormously aroused the enthusiasm on the exploration of organocatalysis. The development of the organocatalytic activation models turned out to be complementary to chiral metal catalysis, and indeed make some asymmetric reactions more practical.

In this section, we choose three important reactions, aldol reaction (C–C bond forming reaction), α-amination of carbonyl compounds (C–N bond forming reaction), and Diels–Alder reaction (simultaneous formation of multiple bonds), to demonstrate how the advent of new activation models and new chiral catalysts significantly improve the synthetic efficiency and make related asymmetric reactions more ideal. A detailed discussion is also conducted by the criterions of ideal asymmetric catalysis introduced above.

The aldol reaction is one of the most important C–C bond forming reactions [38], as the resulting β-hydroxy carbonyl compounds are very useful building blocks.