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TOWARD IDEAL ASYMMETRIC CATALYSIS

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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

Multicatalyst System in Asymmetric Catalysis, First Edition. Jian Zhou.

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:

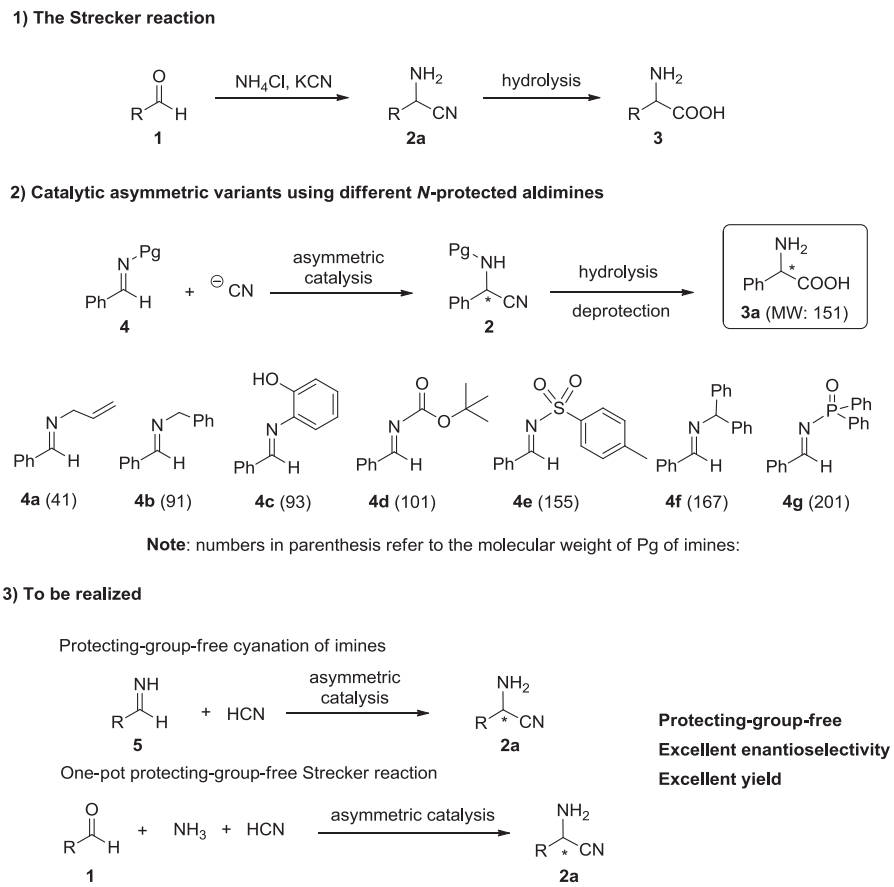
1. **Catalyst Screening and Evolution.** The purpose of this step is to identify a promising chiral catalyst. Usually, intensive screening of chiral catalysts that could be readily available is conducted at this step. If lucky enough, the ideal chiral catalyst which could achieve excellent stereoselectivity 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

directions. One is to introduce an activating group to at least one of the reaction partners to increase the reactivity, which enables the reaction to be run at low temperature to improve the selectivity, and the other is to install a bulky shielding group to enlarge the face discrimination for better enantiofacial control. The substrate modification is an effective and widely adopted approach to improve the selectivity; however, it inevitably decreases the synthetic efficiency, as the introduction and removal of such groups entails at least two extra steps. In addition, the activating group or the bulky shielding group will not present in the final product, which lowers down the atom utilization of the whole process to synthesize a given chiral product and inevitably increases waste generation.

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 nontoxic 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.

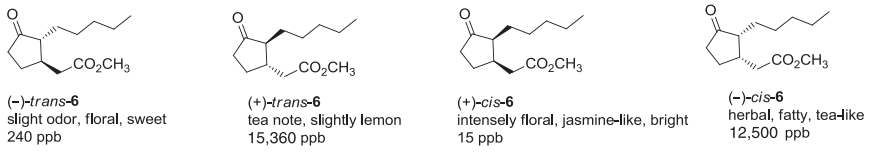
A good example to elucidate the aforementioned dilemma is the catalytic asymmetric Strecker synthesis of α-aminonitriles [10], which are versatile precursors of α-amino acids and diamines. This reaction, discovered by Adolph Strecker in 1850 [11], comprises a one-pot three component condensation of an 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,



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

they 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



Hedione (trans:cis 90:10), present in *Odeur 53* (Comme des Garcons, **1998**, 63%)
Hedione HC (trans:cis 25:75), present in the bestsellers *Pleasures* (E. Lauder, **1995**, 6.3%) and *Juicy Couture* (E. Arden, **2010**, 6%)
Paradisone ((+)-*cis*-**7**), present in *Mystery* (Naomi Campbell, **2003**, 21%) and *Ange ou Demon* (Givenchy, **2006**, 25%)

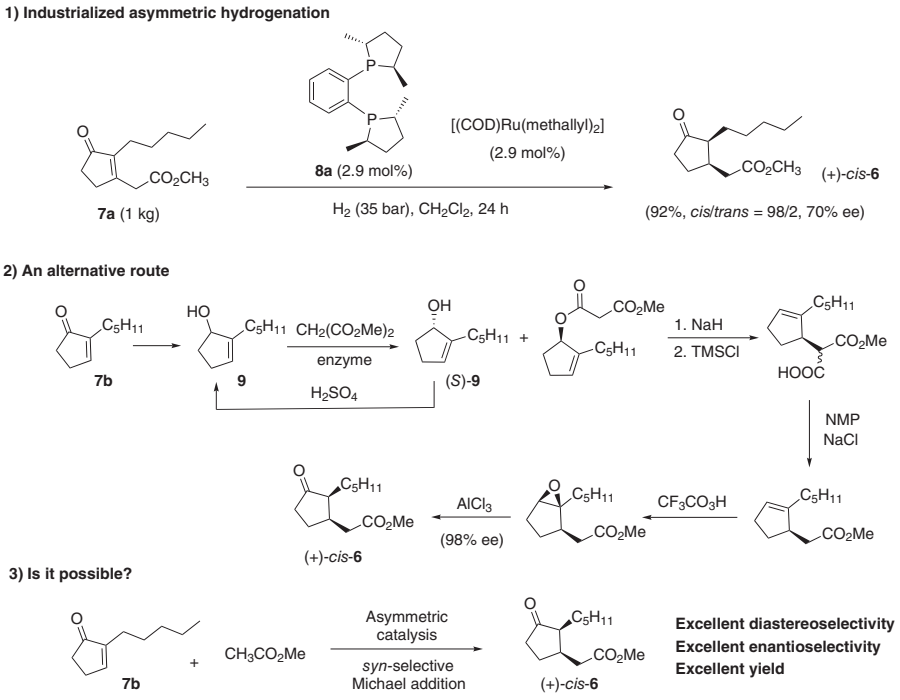
FIGURE 1.1 Methyl dihydrojasmonate **6** and its presence in some brands of perfumes.

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 **6** [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 *cis*-isomers of **6** are much more powerful (about 70 times) than the *trans*, and the (+)-*cis*-**6** proved to be the only stereoisomer that has an odor. Even the (−)-*cis*-**6** is very weak, and more earthy than floral in smell. Acid- or base-induced epimerization at C(2) of the *cis*-isomers is rapid, and the *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 (+)-*cis*-**6**, which is used under controlled $5 < pH < 7$ or stabilized conditions to avoid equilibration. Accordingly, catalytic asymmetric synthesis of (+)-*cis*-**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 **7a** is a straightforward method for the synthesis of (+)-*cis*-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 **8a**/Ru complex could catalyze the hydrogenation in a scale of 1.0 kg, to afford (+)-*cis*-**6** in 92% yield with 70% ee [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.



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 α-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

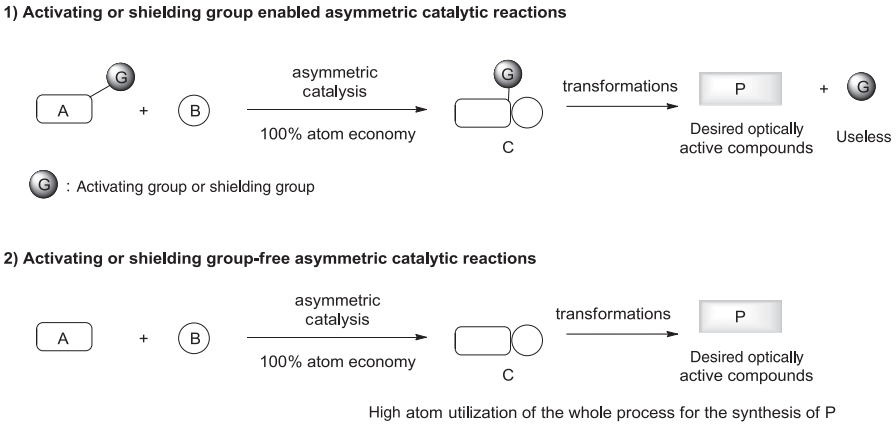
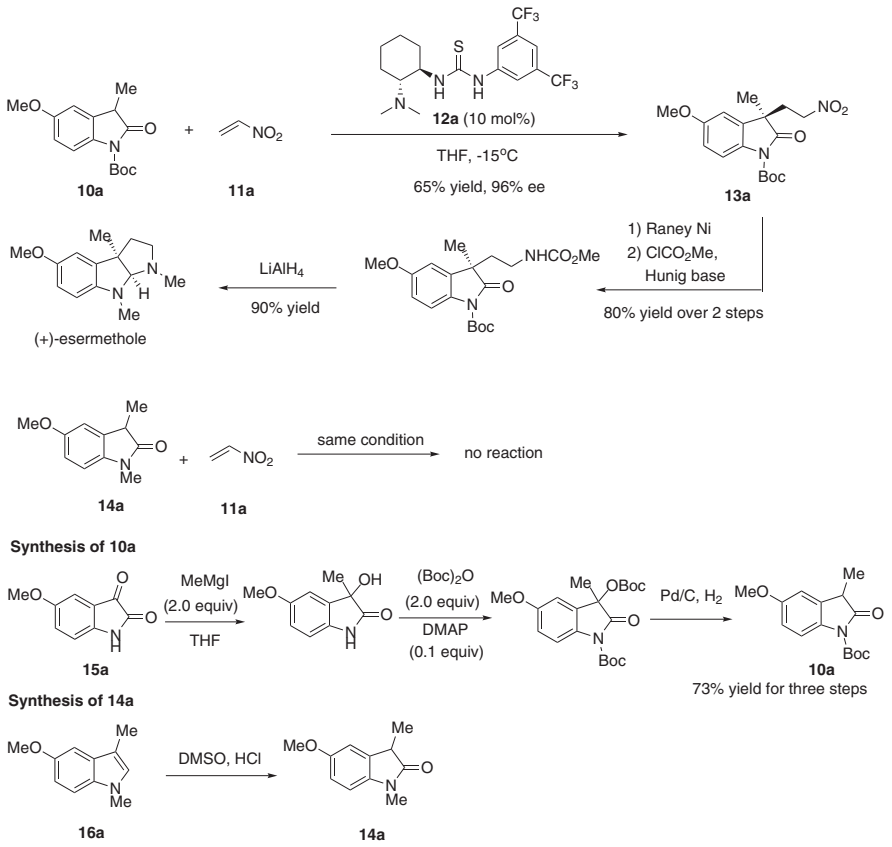


FIGURE 1.2 Toward high atom utilization catalytic asymmetric synthesis.

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 staring 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 $(Boc)_2O$ [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



SCHEME 1.3 The difference between *N*-Boc protected oxindoles and *N*-methyl analogues.

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

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.

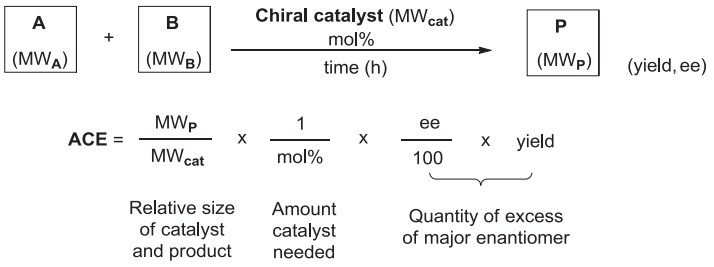
Although the formula proposed by Todd and Richards might be further improved to be generally accepted for the evaluation of the catalyst efficiency, its basic idea is noteworthy. The efficiency of a catalytic asymmetric reaction should be evaluated not only by the enantioselectivity and yield of the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

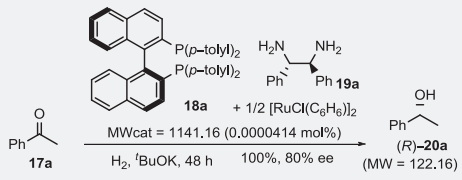
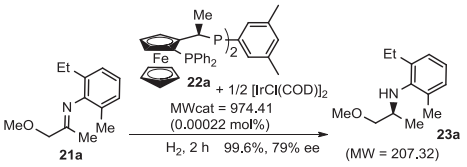
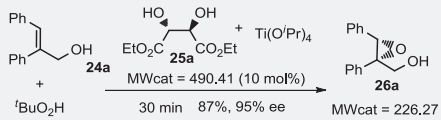
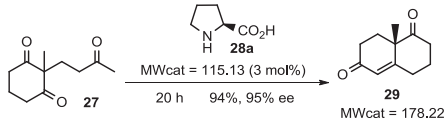
Two important solutions for raising the catalyst efficiency of a given asymmetric reaction should be highlighted. First, the development of low catalyst loading reaction is very important. Even if the chiral catalyst is very expensive, the low catalyst loading could effectively decrease the expense for 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 CEt_3 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

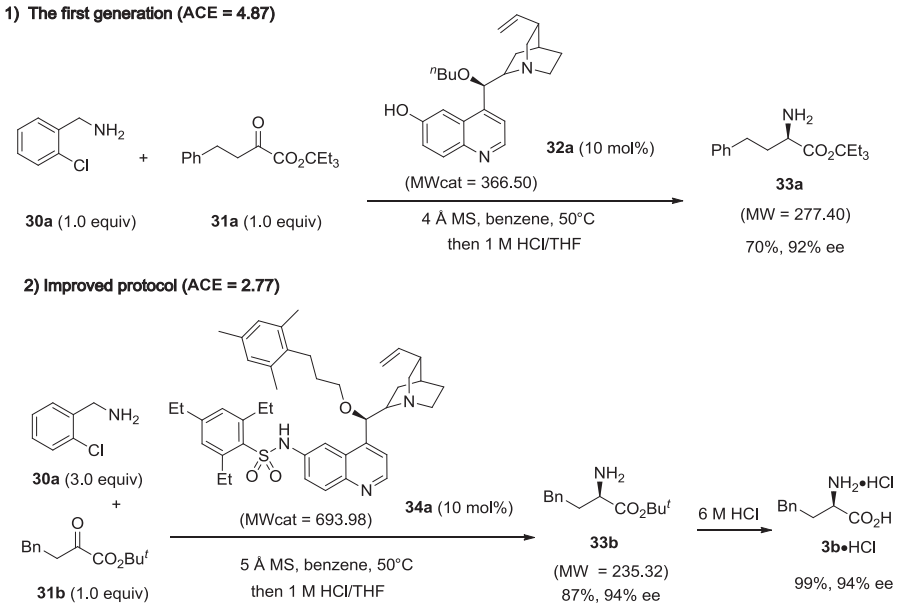


Entry	Representative Reaction	ACE	Cat. Cost [Eur][a]	Cost of Product [Eur][b]	TON (h^{-1})	ACES
1		206,858	119.5	0.000,07	50,322	4310
2		76,096	381.71	0.001	226,364	38,048
3		3.81	0.21	0.012	17	7.62
4		46.1	0.76	0.002,9	1.6	2.31

[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 compatibility, 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 contaminated 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 asymmetric 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

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

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.

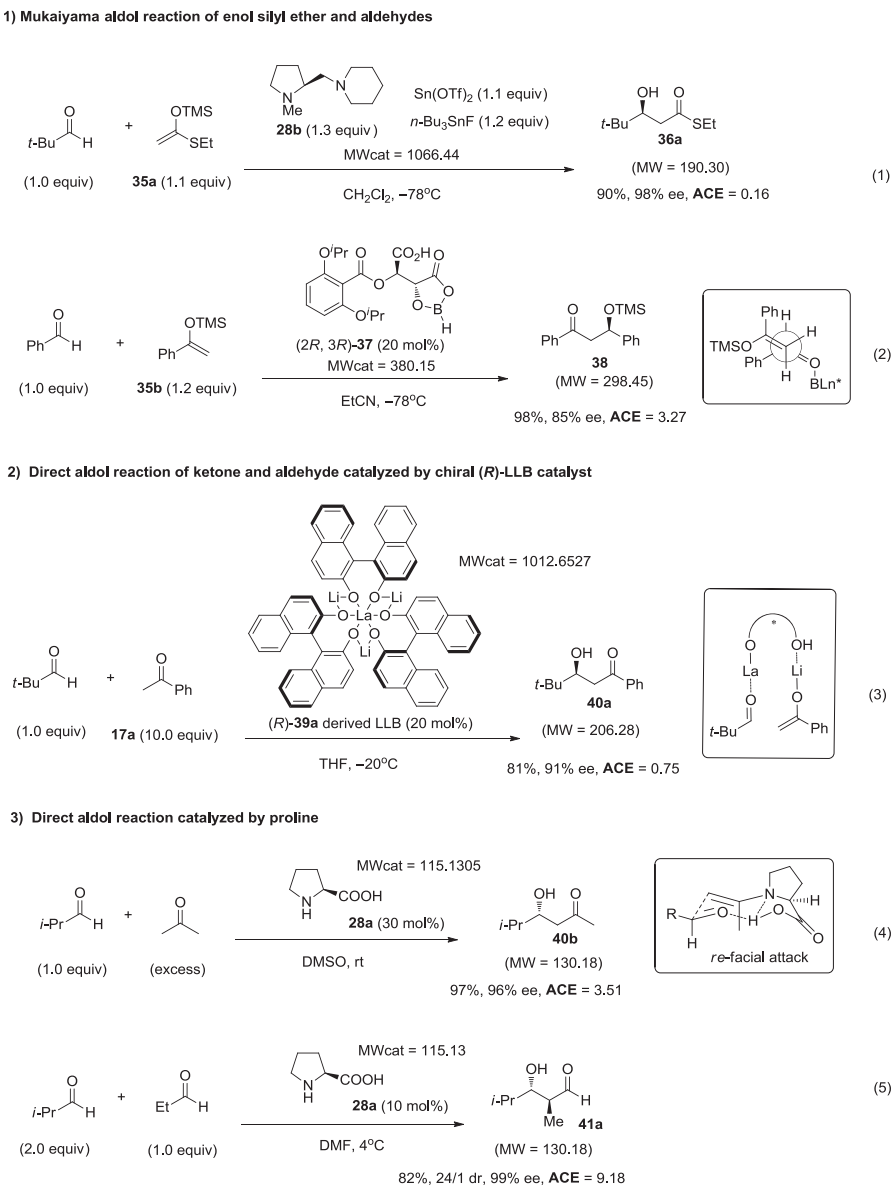
The aldol reaction is one of the most important C─C bond forming reactions [38], as the resulting β-hydroxy carbonyl compounds are very useful building blocks

in organic synthesis. The development of enantioselective processes has a long and continuing history. Initially, the reactions of B, Ti, Si, and other enolates using stoichiometric amounts of chiral sources are intensively studied. Notable examples include seminal research from the groups of Evans [39], Heathcock [40], Masamune [41], and Mukaiyama [42]. To achieve the propagation of chirality, catalytic asymmetric aldol-type reactions using enolate equivalents is then studied. Although many highly enantioselective protocols of such aldol-type reactions have been developed, atom utilization and synthetic efficiency have ample room for improvement, judged by the criterions introduced above. The frontier in this field is to develop direct aldol reaction using aldehydes and unmodified carbonyl compounds. To introduce how the application of new activation model greatly makes this reaction more efficient, four seminar contributions are introduced in Scheme 1.6, with ACE values indicated for the rough comparison and judgment of the synthetic efficiency of these reactions.

By chiral Lewis acid catalysis, namely the use of a chiral Lewis acid to activate the electrophilic aldehydes and realize chiral induction, the first highly enantioselective aldol reaction is developed by Kobayashi and Mukaiyama in 1989 (Eq. 1) [43], which is based on the reactive silyl enol ethers of *S*-ethyl ethanethioate **35a** and achiral pivalaldehyde to afford β-hydroxy thioester **36a**, catalyzed by a chiral promoter consisting of tin (II) triflate, tributylfluorostannane, and chiral ligand **28b**. In 1991, Furuta and Yamamoto utilized a chiral (acyloxy)borane complex to realize a highly enantioselective Mukaiyama aldol reaction of the less reactive ketone enol silyl ethers **35b** with benzaldehyde to give product **38** (Eq. 2) [44]. Compared with conventional asymmetric aldol reactions involving the use of stoichiometric amount of a chiral source, these seminar works constitute a significant breakthrough in this field, which no long require attaching and removing the chiral sources. However, the preconversion of the ketone moiety to the corresponding enol silyl ether necessitates an extra step, and the trimethylsilyl (TMS) group will not present in the final products, although the TMS-protected product might be viewed as a synthon in some cases. Accordingly, the development of a direct catalytic asymmetric aldol reaction, on the basis of unmodified carbonyl compounds (e.g., aldehyde and ketones), is the next goal but proves to be very challenging.

Fortunately, the advent and application of dual activation strategy, namely the simultaneous activation of both the electrophile and nucleophile, paves the way to the first direct intermolecular aldol reaction of aldehydes and unmodified ketones (Eq. 3) [45], which is reported by Shibasaki and coworkers in 1997 using anhydrous bifunctional (*R*)-**39a** derived LLB catalyst (L = lanthanum, L = lithium, B = (*R*)-binaphthol moiety) developed in their group. This is an important contribution, showing the possibility to develop atom- and step-efficient catalytic asymmetric intermolecular direct aldol reactions with a designed chiral catalyst. With this significant advance, the bar is further raised to achieve highly enantioselective direct aldol reactions using low molecular chiral catalysts with high ACE values, in a simple operation.

A breakthrough in the development of catalytic asymmetric direct intermolecular aldol reaction results from the unveiling of the asymmetric enamine catalysis [46], the activation of the nucleophilic aldehydes or ketones via the formation of enamine. Inspired by the pioneering work of Hajos, Parrish, Eder, Sauer, and Wiechert in the



SCHEME 1.6 The evolution of catalytic asymmetric aldol reaction.

proline-catalyzed intramolecular aldol reaction of diketones, List, Lerner, and Barbas reported in 2000 that proline, as a simple secondary amine catalyst, could efficiently catalyze direct aldol reaction of acetone with aldehydes to furnish the desired adducts in good yields and high-to-excellent ee values (Eq. 4) [47]. Based on proline catalysis, Northrup and MacMillan further accomplished the first direct and enantioselective

cross-aldol reaction of aldehydes (Eq. 5) [48], a formidable synthetic challenge on account of (i) the self-aldolization of aldehydes and (ii) the tendency of aldehydes to polymerize under metal-catalyzed condition. In spite of the challenges to be explored, the proline-catalyzed direct intermolecular aldol reaction unambiguously represents enormous strides toward ideal asymmetric catalysis: simple starting materials, cheap and low-molecular-weight catalysts, high ACE values, simple operation, metal-free, and so on.

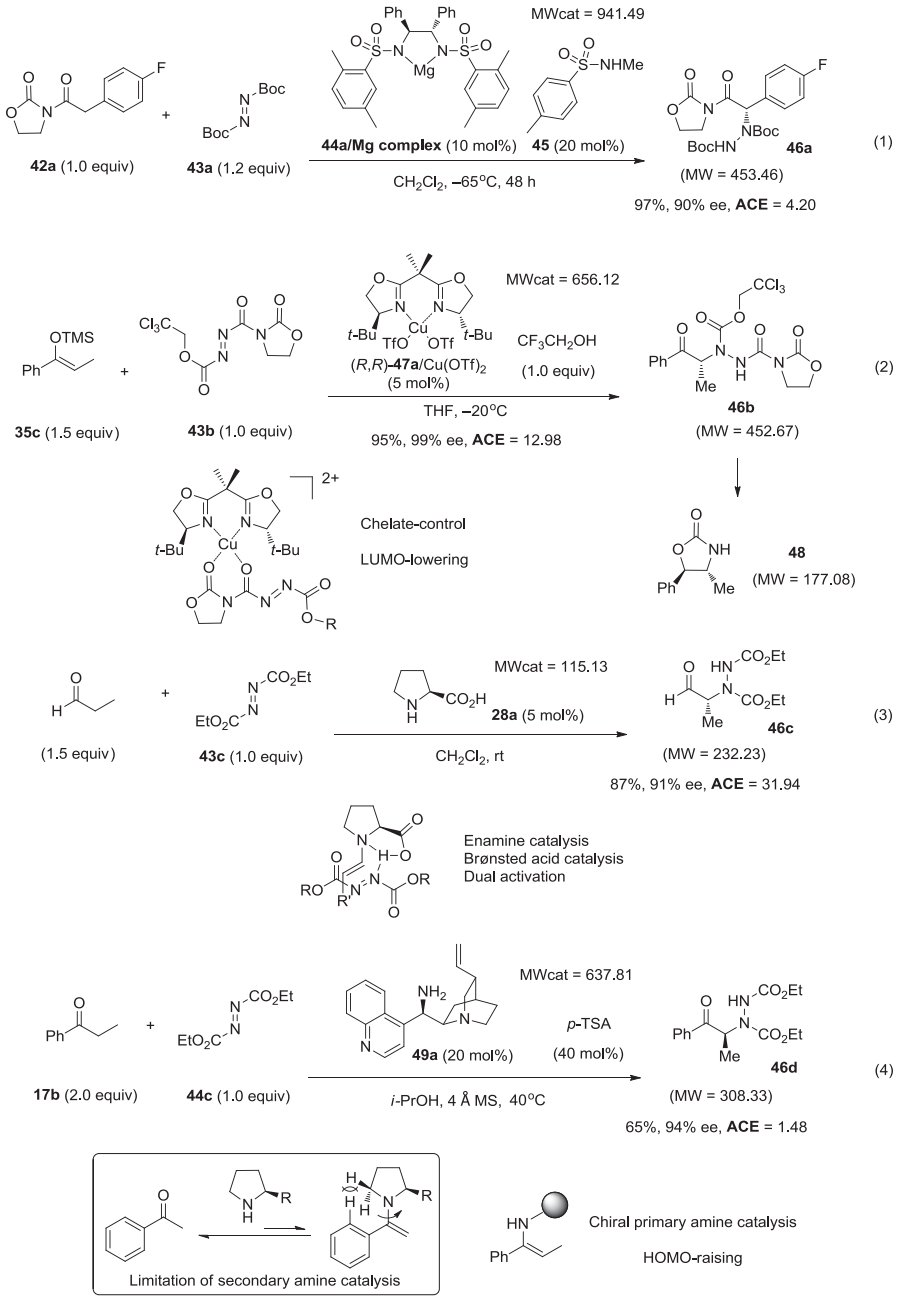
The mechanistic studies on proline catalysis in the aldol reaction establish that the enamine catalysis may be a universal strategy for the catalytic generation of chiral carbanion equivalents from carbonyl compounds, which gives an impetus to develop catalytic asymmetric α-functionalization of aldehydes or ketones in a highly efficient manner that is difficult to be realized by the available chiral metal catalysis.

To further elucidate the dramatic impact of the renaissance of asymmetric enamine catalysis, the electrophilic α-amination of carbonyl compounds is introduced in Scheme 1.7. While this asymmetric C—N bond forming reaction has been intensively studied and turned out to be a powerful strategy for the synthesis of α-hydrazido and α-amino acid derivatives [49], it takes a long journey to make this reaction more practical. In 1986, chiral auxiliary-controlled synthesis based on either preformed chiral enolates is first developed [50], and 10 years later, the first catalytic asymmetric variant is reported (Eq. 1).

Evans and Nelson employed a chiral magnesium bis(sulfonamide) complex to achieve the first catalyzed direct enantioselective enolate-electrophile-type bond formation [51]. The use of *N*-acyloxazolidinone derivatives **42a** is key to realize high enantioselectivity, as the bidentate coordination of substrate with Mg(II) allow stable transition state via chelation control (Eq. 1). Later, the same group employed an alternative strategy, the reaction of enolsilanes **35c** with azodicarboxylates **43b** which is modified with a bidentate auxiliary (Eq. 2) [52]. In both highly enantioselective catalytic variants, although the propagation of chirality is realized, at least one of the reaction partners should be modified with a bidentate oxazolidinone to facilitate the interaction with chiral metal catalysts. It goes without saying that the installation and removal of such an appendage incur extra work and release more waste, and greatly decreased the atom utilization, as evidenced by the conversion of the amination adduct **46b** to oxazolidinone **48**, with only 39% of atoms of **46b** remained.

With the establishment of enamine catalysis, List and Jørgensen independently pioneered the direct α-amination of aldehydes by proline catalysis (Eq. 3) [53]. It would be awe-stricken to see how the enamine catalysis greatly improved the synthetic efficiency of this important asymmetric C—N forming reaction: cheap and simple catalyst and reagents, high yield and almost perfect enantioselectivity, mild reaction condition, no complicated manipulation, and open to air. The only spitball on this reaction is the use of azodicarboxylates as the electrophile, as a substantial amount of atoms will be lost in the product elaboration, but this is the limitation of this electrophilic amination itself.

To expand the substrate scope of the carbonyl compounds to aryl ketones, the precursor of the enolsilanes **35c** used in Evans's report (Eq. 2), chiral primary amine



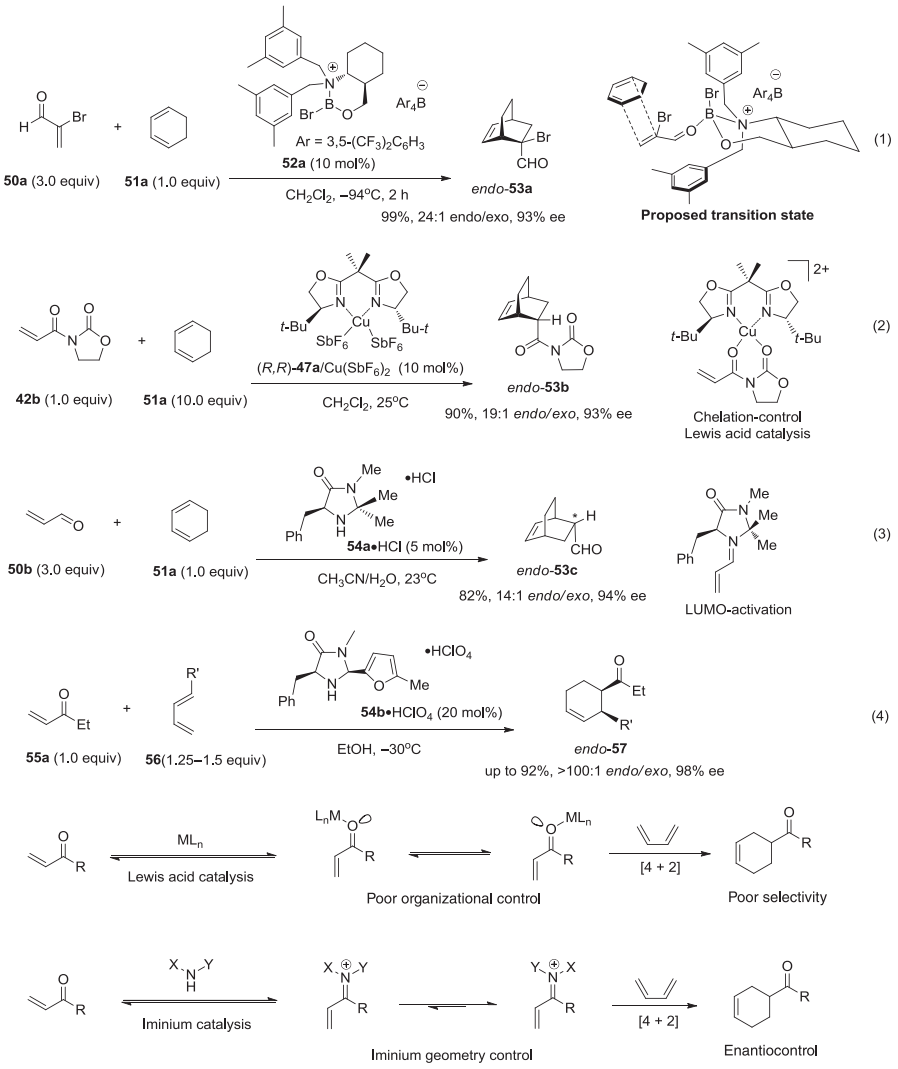
SCHEME 1.7 The evolution of electrophilic amination reaction.

catalysis demonstrates its unique advantages in the generation of nucleophilic enamines from aryl ketones, due to its reduced steric hindrance [54]. Chen and coworkers first identify that 9-amino-9-deoxyepicinchona alkaloid **49a** as a powerful catalyst for this reaction (Eq. 4) [55]. Comparing the improved protocol with the initial report using enolsilane as the enolate equivalent shown in Eq. 2, one can easily understand how the synthetic efficiency of catalytic asymmetric α-amination reactions is greatly enhanced by the implementation of asymmetric enamine catalysis.

Another convincing example to demonstrate the exceptional power of the discovery of new activation models to realize ideal asymmetric catalysis is the evolution of asymmetric Diels–Alder reaction, which is probably the most powerful organic reaction in chemical synthesis, allowing facile construction of substituted carbocycles from simple substrates [56]. While notable progress has been made in the development of chiral Lewis acid catalyzed asymmetric Diels–Alder reaction using reactive cyclopentadiene, the corresponding process using less reactive dienes such as 1,3-cyclohexadiene and heavily substituted acyclic dienes proves to be very challenging.

In 1996, Hayashi and Corey developed a cationic oxazaborinane catalyst **52a**, obtained by the exchange of a bromide with a non-coordinating tetraarylborate, which are much more Lewis acidic than the previously studied neutral chiral Lewis acid [57]. Such a new class of super-reactive chiral Lewis acid catalyst proves to be very reactive and enantioselective, which promotes the Diels–Alder reaction of 2-bromoacrolein and 1,3-cyclohexadiene in excellent stereoselectivity (Eq. 1, Scheme 1.8). In 1999, by means of chelation control, Evans and coworkers further reported a chiral bisoxazoline derived copper complexes to promote the reaction of acrylimide **42b** and 1,3-cyclohexadiene **51a** to give the desired product in excellent yield and stereoselectivity (Eq. 2) [58]. An advantage of this process is to secure excellent diastereo- and enantioselectivity at room temperature, which greatly simplifies the operation and reduces energy consumption.

A breakthrough in the development of ideal catalytic asymmetric Diels–Alder reaction emerges with the introduction of iminium catalysis [59] in 2000. MacMillan and coworkers reported the use of a secondary amine **54a**·HCl as a powerful LUMO-lowering catalyst for the highly enantioselective Diels–Alder reaction of α,β-unsaturated aldehydes with a broad range of dienes [60]. For example, the reaction of acrolein **50b** and 1,3-cyclohexadiene **51a** proceeds well at room temperature to give product *endo*-**53c** in 82% yield and excellent selectivity (Eq. 3). It is really amazing that such a cheap low-molecular-weight amine catalyst (the cost of catalyst **54a**·HCl is estimated by authors to be $6 per 50 g) enables the Diels–Alder reaction involving challenging dienes to meet the criterions of ideal asymmetric catalysis to a great extent: apart from the excellent selectivity and yield, the reaction is performed in aqueous solution at room temperature. More remarkably and importantly, MacMillan and coworkers further applied iminium catalysis to develop the first general enantioselective catalytic Diels–Alder reaction of simple α,β-unsaturated ketones **55a** (Eq. 4) [61], a long-standing goal that has never been realized by chiral Lewis acid catalysis. Usually, high level of stereoselectivity is achieved by using dienophiles such as aldehydes, esters, quinones, and bidentate chelating carbonyls in the Lewis acid mediated Diels–Alder reactions, as the lone pair discrimination in



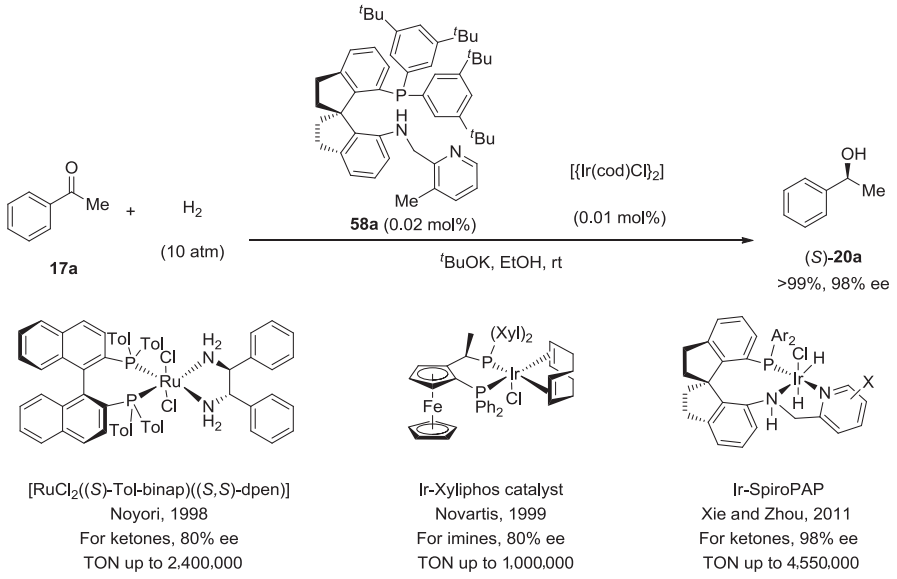
SCHEME 1.8 The evolution of asymmetric Diels–Alder reaction.

the metal coordination step is efficient owing to the suitable steric, stereoelectronic, and chelation control. In contrast, the intrinsic deficiency associated with the Lewis acid activation of simple acyclic α,β-unsaturated ketones is the poor organization control, due to the small difference of the steric and electronic environment of the participating lone pairs of ketone carbonyl moiety. The powerfulness of the iminium catalysis lies in the fact that, by elegant balance the interaction of catalyst and substrate, the selective formation of a tetrasubstituted iminium ion might be realized to achieve excellent enantiofacial control in the following cycloaddition reaction.

In retrospect, and considering the historical advances in the aforementioned three important types of asymmetric reactions, one can fully understand how important the discovery of new activation models to make asymmetric catalysis more efficient and environmentally benign. On the other hand, it is evident that each known activation model has its advantages and limitations. While the advent of asymmetric enamine catalysis and iminium catalysis has significantly improved the efficiency of a number of organic transformations based on simple aldehydes and ketones, both activation models are unable, at least currently, to extend to other types of functionalities. Even carbonyl compounds that are difficult to undergo imine formation reaction, for example, α-disubstituted ketones, proved to be problematic substrates for reaction design. In addition, high catalyst loading is another issue waiting for further improvement.

On the contrary, the chiral metal catalysis seems to be a general solution to activate different kinds of electrophiles, as different kinds of metal catalysts can function as either Lewis acid catalysts or transition metal catalysts, but its limitation is obvious as well. Apart from the intrinsic problem of the contamination of final optically active products with heavy metal cations, how to realize efficient and direct influences on the stereochemical outcome in metal-catalyzed processes is very challenging, as the distance between the stereogenic centers of the chiral ligand and the reactive center of the substrate is usually more than five bonds in the transition state organized by coordination. In direct contrast, the distance can be reduced to three covalent bonds in the case of asymmetric enamine catalysis and iminium catalysis, as evidenced in Schemes 1.6, 1.7, and 1.8. Accordingly, it usually requires increasing the shielding group or the rigidity of the chiral ligand and the use of substrates capable of bidentate coordination to reduce disadvantages such as rotation and flexibility in enantiofacial control in a metal-catalyzed reaction, which leads to the increase of difficulty in the synthesis of chiral ligands and finally decreased the synthetic efficiency in most cases. Another issue concerning the transition metal catalysis is the prevention of the formation of inactive dimers or trimers of the metal catalysts under the reaction condition, which is another important issue to improve the efficiency of transition metal catalysis. Traditional methods include the use of additives [62], or the immobilization of catalysts, the use of a bulky counteranion, and the introduction of a bulky or rigid ligand [63] to prevent catalyst dimerization. However, the development of strategy in ligand design to overcome this challenge and make chiral metal catalysis more powerful is still very much in demand.

For example, Xie and Zhou recently achieved the asymmetric hydrogenation of ketones with the highest TON (up to 4,550,000), by using a chiral Ir complex derived from an elegantly designed spiro aminophosphine ligand **58a**, with a pendant pyridinyl group as an auxiliary coordination group to prevent catalyst deactivation via formation of dimeric complexes (Scheme 1.9) [63]. Therefore, the newly invented chiral Ir complex achieved significantly higher TON numbers in ketone hydrogenation, than the previous landmark work: the diphosphine/diamine ruthenium catalyst reported by Noyori et al. [25] and the iridium ferrocenyl catalyst Ir-(*R*,*S*)-Xyliphos developed by a team from Novartis [64], both with TONs over a million reported.



SCHEME 1.9 The evolution of high TON transfer hydrogenation of ketones.

While the discovery of new activation models, together with the development of new powerful chiral catalysts based on the known activation models, will gradually make up the deficiencies described and contribute to the development of ideal asymmetric catalysis, it is almost impossible for any of an activation model to meet all the challenges mentioned above. In addition, it should be noted that the number of activation models might be limited, and the development of super chiral catalysts is cost-intensive and time-killing. A frustrating fact, to some extent, is that only a handful of privileged chiral ligands and organocatalysts have been available, after almost 50 years' intensive studies with devotion from hundreds of thousands of researchers. In view of these challenges, synthetic chemists in the field of asymmetric catalysis pay great attention to the mimicking of enzymatic catalysis and most importantly, the utilization of the key principles, combining concepts, used in biological systems to develop new asymmetric reactions and processes, which will be discussed in the next section.

1.4 BORROW IDEAS FROM NATURE

Catalysis is not a human invention, as catalytic processes have existed in nature for a long history. Unambiguously, evolution through nature selection over millions of years has indeed enabled ideal asymmetric catalysis in living cells, as all the reactions were conducted in aqueous solution at room temperature, with high catalytic turnovers and unerring stereospecificity. Most strikingly, the multienzymatic systems in cell accomplish extremely efficient one-pot tandem catalysis to transform simple materials

to complex molecules with perfect control of selectivity via a serial of coupled reactions. Such a remarkable efficiency can be straightforwardly exemplified by the enzymatic synthesis of 14-membered macrolide 6-deoxyerythronolide B (DEB) [65], which is the precursor of the antibiotic erythromycin (Figure 1.3). In theory, this complex molecule, with 10 stereogenic carbon centers, should have 1024 isomers; however, the molecular assembly line, in which multi-enzyme 6-deoxyerythronolide B synthase proteins work in succession, enables the stereospecific building up of molecular complexity by joining, via a thioester linkage, small organic acids such as acetic acid.

6-Deoxyerythronolide B has for sure aroused tremendous attention from the synthetic community, owing to the challenges in chemical synthesis. The most concise man-made total synthesis of 6-deoxyerythronolide B reported to date, consisting of 14 steps from 2-methyl-1,3-propandiol (longest linear sequence) and 20 total steps, was reported in 2013, in which Krische and coworkers applied two elegant protocols of highly enantioselective catalytic asymmetric alcohol CH-crotylation via transfer hydrogenation, developed in their own group, for the synthesis of two important fragments **I** and **II** [66] (Scheme 1.10). However, the use of step-by-step purification (18-column chromatography involved), several protection and deprotection manipulations, toxic reagents such as OsO_4, and large amounts of metal catalysts in key steps suggests the enormous room for human beings to further improve the synthetic efficiency, as compared with the biosynthetic pathway.

It has long been chemists' endeavors to draw inspiration from nature's synthetic processes to design and synthesize enzyme mimics [67], which imitate characteristic features of enzymes that facilitate efficient catalysis, including (1) high enzyme-substrate binding affinities, (2) high catalytic turnovers, (3) excellent selectivity (chemo-, regio-, diastereo-, and enantioselectivity), and (4) substantial rate accelerations as compared to uncatalyzed processes. Investigation of activation models and biosynthetic pathways in Nature offers ample opportunities for synthetic chemists to achieve similar efficient, or even more efficient, transformations. Among the principles and concepts used in living cells, the cooperation of two or more catalysts (or catalytic moieties within an active site of enzyme) to facilitate a certain transformation is prevalent. In this section, some emblematic cooperation models are introduced to demonstrate the powerfulness of cooperation of multiple catalysts.

A generally accepted paradigm in enzymatic catalysis is the capacity of enzymes to bind transition states and intermediates in preference to either starting materials or products, in which the cooperation of different H-bonding donors such as hydroxy groups and amide N—H bonds plays an important role. The hydrogen-bond interactions between substrates and the active site of enzymes align reactive chemical groups and hold them close together, which give the reaction intramolecular character such as an effective increase in concentration of the reagents and favorable orientation and proximity. For example, by the H-bonding interaction networks provided by the cooperation of a number of H-bond donors of several types, the transition state of the production of tetrahydrofolate, an important coenzyme for the transfer of one carbon units, from the folic acid metabolite dihydrofolate via a hydride transfer to the imine moiety is organized in an optimized geometrical arrangement [68]. As shown

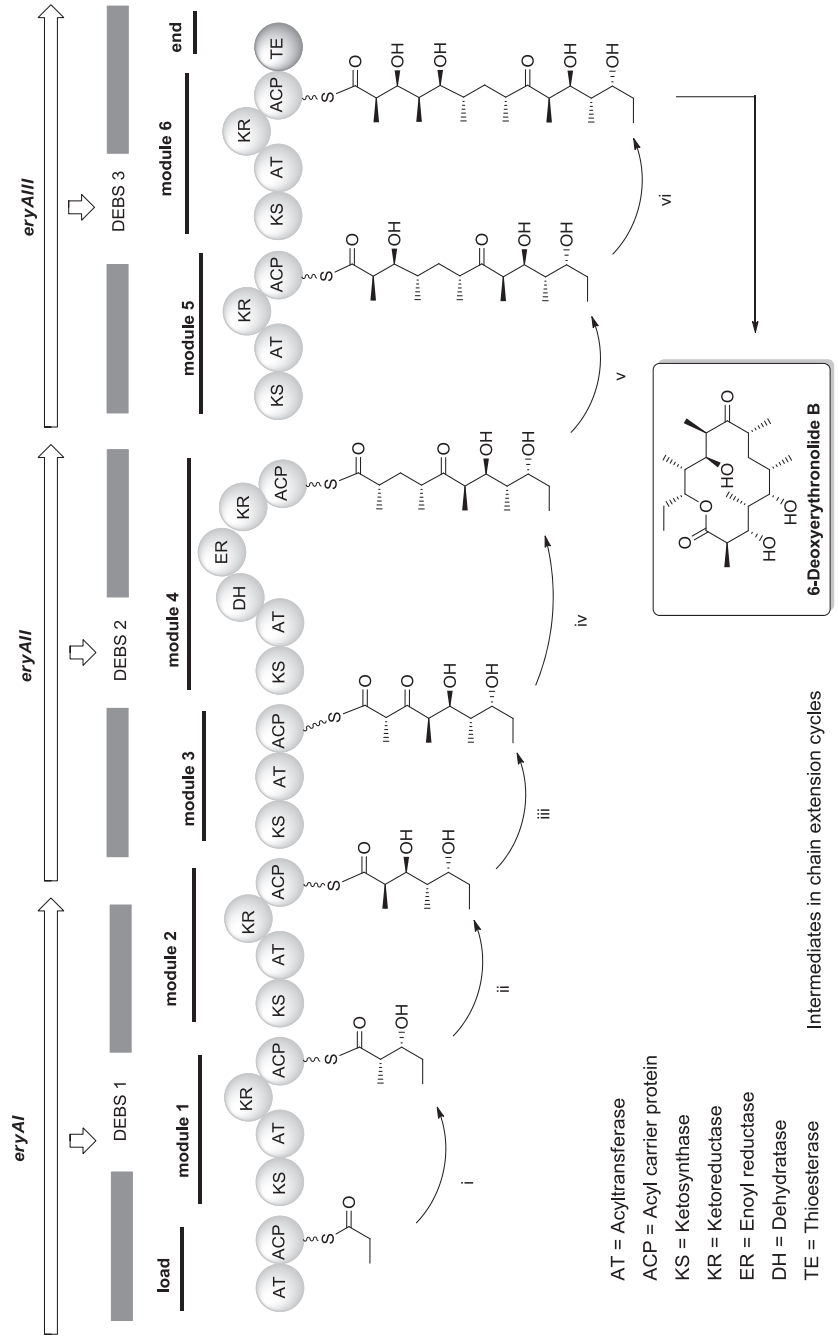
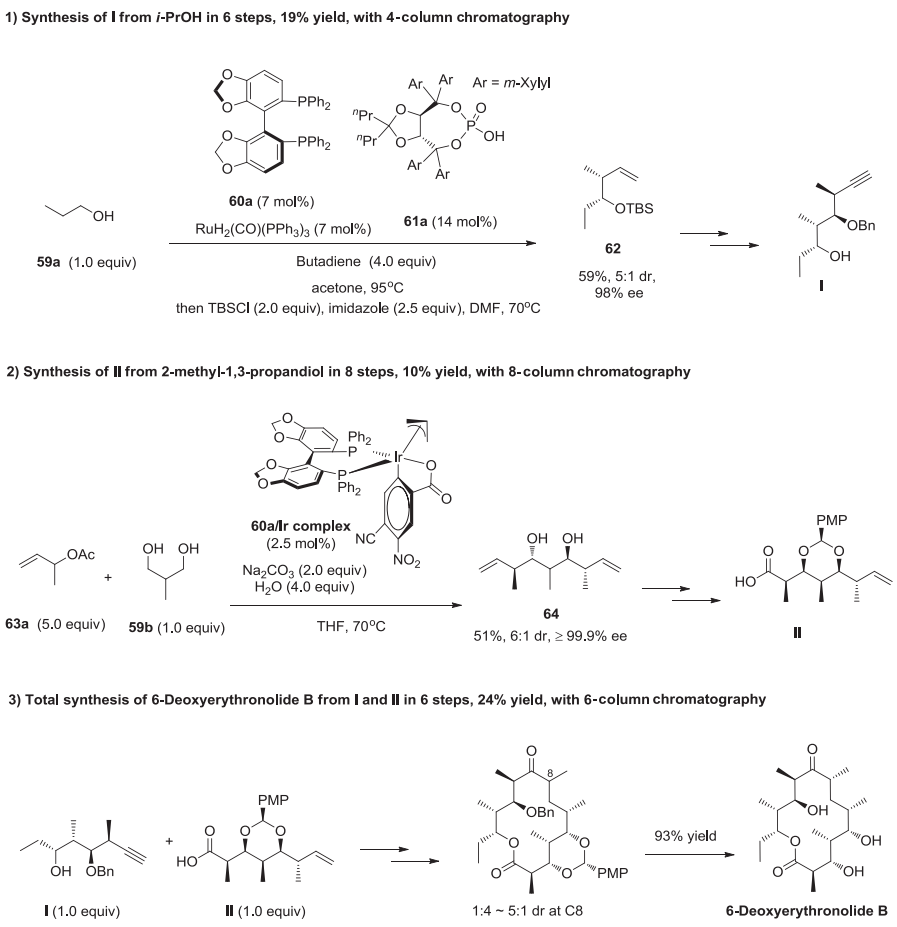


FIGURE 1.3 Domain organisation of the erythromycin polyketide synthase.



SCHEME 1.10 The most concise man-made route to 6-deoxyerythronolide B.

in Figure 1.4, in the active sites of the enzyme dihydrofolate reductase, the H-bonding network binds dihydrofolate tightly, and activates it toward hydride addition through protonation of the imine. In addition, the synergistic catalysis is achieved by the cooperative H-bonding interaction, which binds the coenzyme $NADP^+$, catalytically activates the hydride source NADPH, delivers the hydride, produces tetrahydrofolate, and regenerates $NADP^+$.

Another remarkable type of the cooperation of multiple hydrogen bonds is to form an enzymatic oxyanion hole in many catalyzed reactions in enzymes such as hydrolase, lipase, protease, and esterase. The characteristic function of the oxyanion hole is to stabilize a high-energy tetrahedral intermediate or transition state featuring a negatively charged oxygen by the simultaneous donation of two or more hydrogen

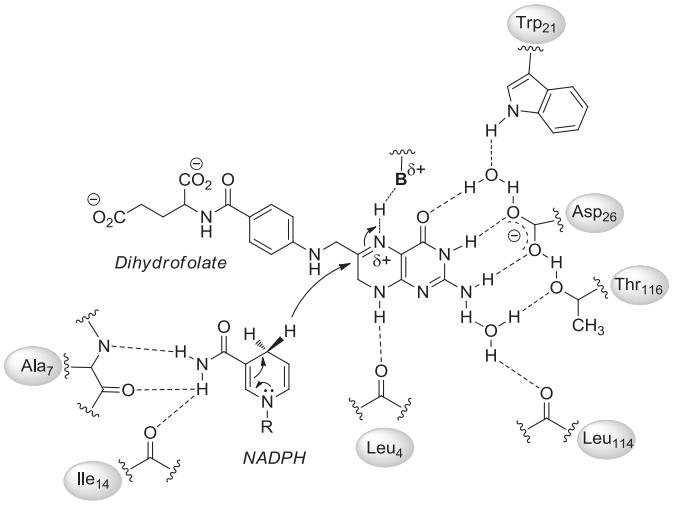


FIGURE 1.4 The multifunctional H-bonding networks in dihydrofolate reductase.

bonds in the active sites [69]. A good example to demonstrate the powerfulness of the oxyanion hole is the chorismate mutases mediated [3,3]-sigmatropic Claisen rearrangement of chorismate to prephenate (Figure 1.5), which is a part of the Shikimate pathway [70]. It is believed that the outstanding rate acceleration effect provided by these enzymes (10^6) is derived from multiple non-covalent interactions, which not only arrange the substrate in the favorable conformation for rearrangement, but are also able to stabilize developing charges in the transition state. It is worth mentioning that in this case, the oxyanion hole formed by positively charged arginine residues, assisted by the π-interaction between the phenyl group of a phenylalanine and the positively charged double bond, contributes to the transition state stabilization.

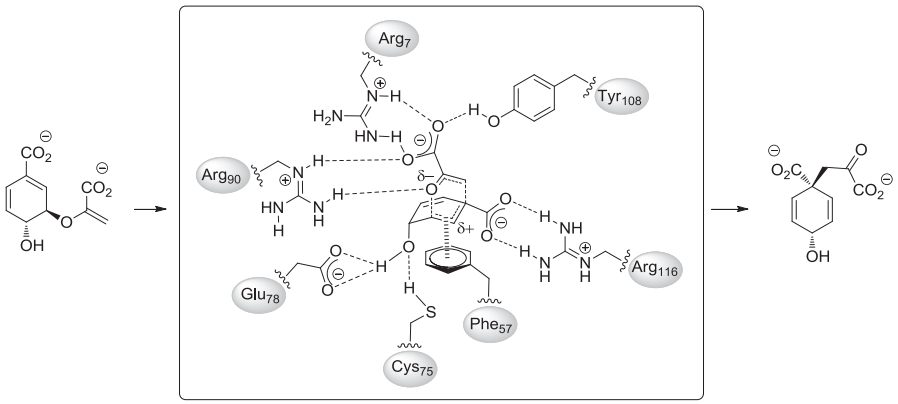


FIGURE 1.5 Chorismate mutase enzymes catalyzed Claisen rearrangement.

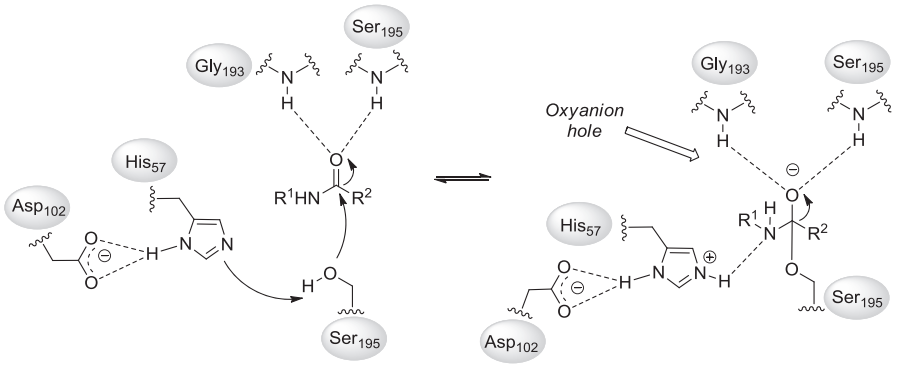


FIGURE 1.6 Synergistic catalysis in serine protease enzymes.

The oxyanion hole is able to cooperate with general base catalysis to realize highly efficient catalytic reactions. A well-known example is the cooperative catalysis observed in serine protease, as shown in Figure 1.6 [71]. Concurrent with the stabilization of the tetrahedral negative oxygen anion by the oxyanion hole created by backbone hydrogens of both Gly_{193} and Ser_{195}, the histidine moiety of the active site accepts a proton from the serine residue, which allows the serine as a nucleophile to attack the amide bond of the substrate. In effect, serine proteases preferentially bind the transition state and the overall structure is favored, lowering the activation energy of the reaction.

This mechanism includes donation of a proton from serine (a base, pK_a 14) to histidine (an acid, pK_a 6), which is possible due to the local environment of the bases. Such concerted acid–base catalysis is also a common enzymatic mechanism, owing to the ability of enzymes to arrange several catalytic groups around their substrates. General acid/base catalysis may donate and accept protons in order to stabilize developing charges in the transition state. This typically has the effect of activating both the nucleophilic and electrophilic reaction partners, or stabilizing leaving groups. Histidine is often the residue involved in these acid/base reactions, since it has a pK_a close to neutral pH and can therefore both accept and donate protons.

A C—C bond forming reaction is also introduced to demonstrate the effectiveness of the cooperation of toxyanion hole with general base catalysis, as shown in Figure 1.7. Strikingly, the Michael addition of acetylacetone to acrolein in the active site of *Candida antarctica* lipase B Ser_{105}Ala proceeds eight orders of magnitude faster than the corresponding uncatalyzed process [72]. The high rate acceleration is partly resulted from the stabilizing effect of the oxyanion hole formed by Gln_{106} and Thr_{40}, which could stabilize the formation of an enolate by three hydrogen bonds to the carbonyl oxygen of the acrolein and organize the two substrates to be close to each other in the active site, and partly from the simultaneous activation of the nucleophilic acetylacetone by the basic moiety of His_{224}.

Apart from the cooperation of organic catalyst moieties in the active sites of enzymes, the concert effects of two or more metal cations play an important role in the enzymatic catalysis as well [73]. A famous type of homobinuclear metalloenzymes

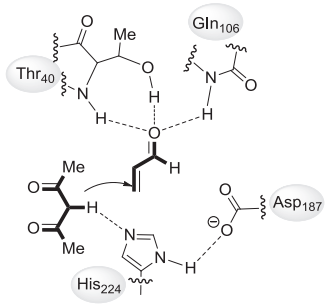


FIGURE 1.7 A hypothetical dual activation model.

are catechol oxidases (COs), which are ubiquitous plant enzymes that catalyze the oxidation of a wide range of *ortho*-diphenols into *ortho*-quinones using oxygen [74]. They belong to the family of type-3 copper proteins, containing a binuclear copper(II) active site.

One of the plausible catalytic cycles for catechol oxidase activity is shown in Figure 1.8. Mechanistic studies have demonstrated distinct roles for each copper center. First, a catechol substrate coordinates to the dinuclear COs in a monodentate fashion on one Cu(II) center, which leads to an interaction between the remaining phenol group of the catechol substrate and the hydroxy group bound to the second Cu(II) center (arising from cleavage of the initial hydroxo bridge). Then the proton transfer occurs followed by displacement of a water molecule, which results in the formation of the bridging coordination of the catecholate to both metal binding sites for further oxidation.

A good example to show the cooperative effects of two different metal cations in a metalloenzyme is the red kidney bean purple acid phosphatases (kbPAPs), the crystal structure of which displays a heterobinuclear $Zn^{II}Fe^{III}$ core (Figure 1.9) [75].

In the active site, located in the carboxyl-terminal domain, the distance between the two octahedral metal ions are bridged monodentately by Asp_{164}. In the hydrolysis of phosphomonoesters, the phosphate group of the substrate binds zinc in a monodentate fashion by displacing the presumed exchangeable water ligand, followed by the intramolecular nucleophilic attack of the hydroxy group bound to the terminal Fe^{III} center on the phosphorus P—O bond, which is activated by the electrophilic zinc ions, to form a pentacoordinate intermediate, and the P—O bond opposite the hydroxide ion attack breaks to form the leaving group and phosphate. In the local environment of the enzyme, the three histidines (His_{202}, His_{295}, and His_{296}) arranged near the metal centers can interact with the phosphate through H-bonding interaction to assist the releasing of an alcohol molecule. The characteristic features of the respective roles of the two metal centers include the formation of assisted intramolecular reaction, together with a favorable geometry that allows the stabilization of the intermediate by both metal centers.

Different from the above activation (fixation) models of the substrates by two metal ions, another example to illustrate the assistive effects of two metal centers

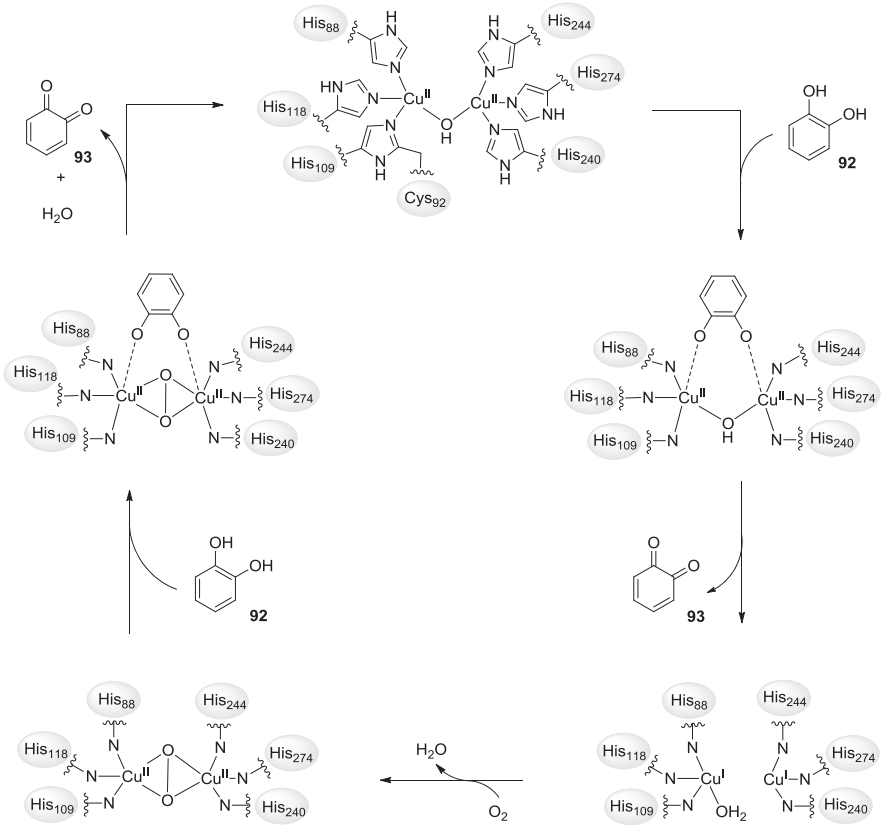


FIGURE 1.8 Proposed catalytic cycle for catechol oxidase activity.

is the Cu—Zn superoxide dismutase (SOD), which is composed of two identical subunits, each containing in its active site an imidazolate-bridged heterobinuclear $Cu^{II}Zn^{II}$ core [76]. Although only the copper center is involved in the catalytic cycle, as shown in Figure 1.10, it is proposed that the coordination of the zinc ion to the imidazole moiety might helpfully assist the protein in adopting the required coordination environment and confers stability to the protein, which is highly stable to heat and is active in a broad range of pH values (4.5–10).

An interesting example to demonstrate the versatility of cooperation catalysis in enzymatic reactions is the aldolases, a specific group of lyases that typically catalyze the stereoselective addition of a ketone donor to an aldehyde acceptor [77]. According to their mechanism, the identified aldolases could be classified by two distinct types. As shown in Figure 1.11, type I aldolases are generally found in higher plants and animals, and activate the donor ketone through enamine catalysis, initiated by the imine formation between the primary amine moiety of Lys_{229} and ketone substrate. On the other hand, type II aldolases are found in bacteria and fungi, which contain a

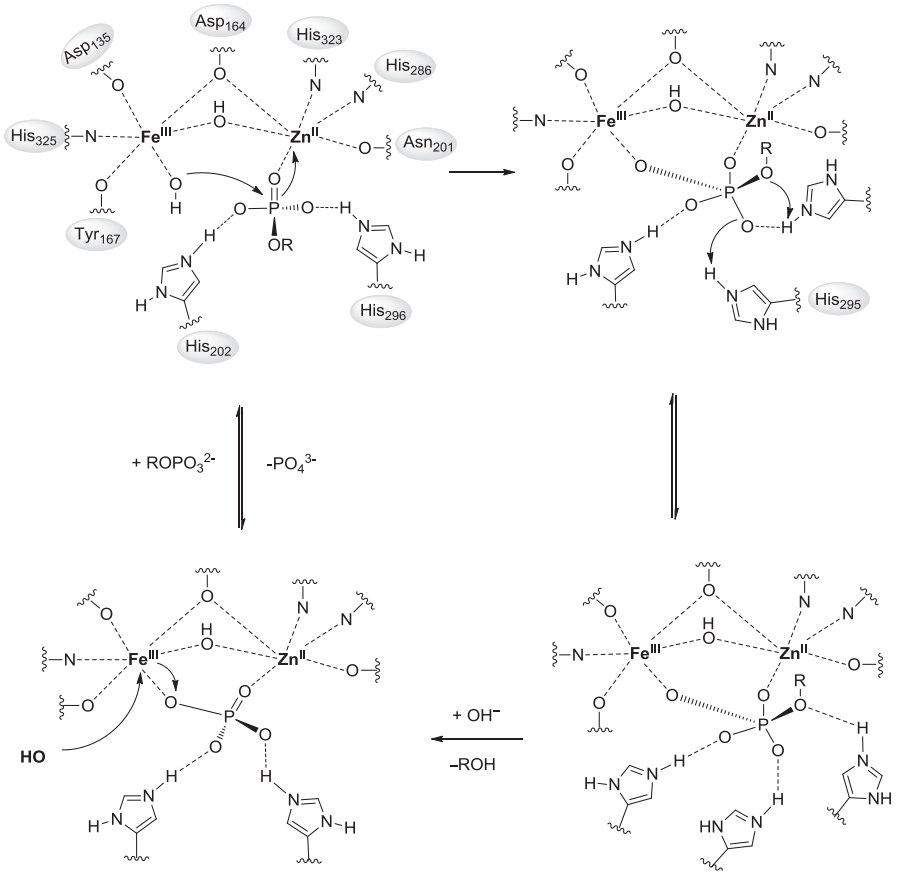


FIGURE 1.9 The cooperation of a Zn(II) and a Fe(III) for phosphate ester hydrolysis.

Zn(II) cofactor in the active site. The zinc ion, coordinated to three histidine residues, polarizes the carbonyl donor to generate the active enolate. In type I aldolases, the primary amine moiety of Lys_{107} helps the fixation of the aldehyde donor through the formation of a phosphate, which contributes to a favorable reaction direction. In contrast, in type II aldolases, there is not only a tyrosine residue that activates the electrophilic carbonyl by offering a proton to stabilize the developing charge, but also a carboxylate of glutamate residue which assists the deprotonative activation of the ketone donor.

From the aforementioned examples, one can have a brief view of the typical cooperation models in enzymatic catalysis. According to the types of the catalysts (catalyst moiety), cooperation can be classified into that of two or more organic catalyst moieties, metal ions, or the combination of organocatalysts and metals. Both organic and metal catalysts could be further divided into many types. Accordingly, it can be reasonably deduced that the combination models in enzymatic catalysis is a

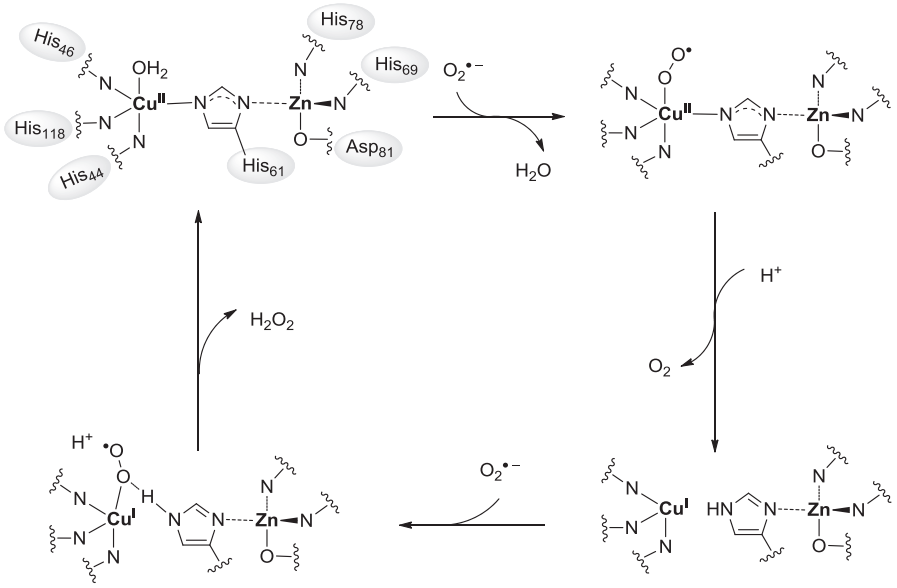


FIGURE 1.10 The cooperation of Cu(II) and Zn(II) in superoxide dismutase.

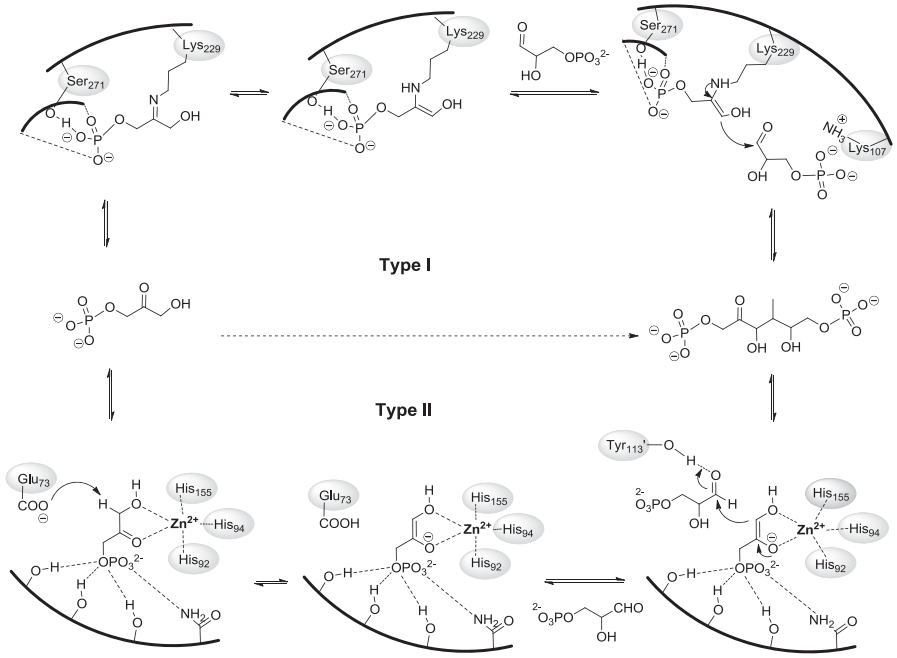


FIGURE 1.11 The two types of aldolase mechanisms.

huge number, perhaps countless. The understanding, mimic, and utilization of such cooperation in living cells to improve the synthetic efficiency of known protocols and to realize previously unattainable catalytic asymmetric transformations have become the frontier in the asymmetric catalysis, which offers golden opportunities for discovery.

1.5 CONCLUSION

Tremendous strides have been made over the past 50 years in the development of highly enantioselective catalytic asymmetric reactions. The major current challenge in the field of asymmetric catalysis is to improve synthetic efficiency to meet the standard of ideal synthesis, namely the development of ideal asymmetric catalysis, for the sustainable development of modern society. One effective way to develop ideal asymmetric catalysis is to invent powerful and practical chiral catalysts. Unfortunately, the discovery of a privileged chiral catalyst [78] is usually tedious, time- and labor-consuming, and often depends on good luck. Accordingly, inspired by the versatile cooperative catalysis in enzymatic reactions, the combination of different catalysts to realize unattainable synthetic efficiency and stereoselectivity by mono-catalysis has received much attention. After almost 20 years' investigation, multiple catalyst systems have demonstrated their powerfulness in (i) achieving some difficult but very useful asymmetric reactions and (ii) allowing the one-pot synthesis of complex molecules with high selectivity from simple starting materials in an almost biomimetic-like way. The success of these pioneer works introduced in this book from Chapter 2–10 has suggested the great potential of multiple catalyst systems to surmount the challenges mentioned above to accomplish ideal asymmetric catalysis.

However, there lacks a book to systematically summarize the exciting results achieved by multicatalyst systems. Having witnessed significant research activities associated with the application of multiple catalysts in asymmetric catalysis, the authors feel it necessary and urgent to write this book to summarize the recent and important discoveries and activities in this area. This will afford wonderful opportunities for readers to be aware of the new and important field and attract more students and chemists to engage in this research field. Moreover, the knowledge and information will also provide an educational opportunity to the public what asymmetric catalysis has achieved and the direction of this important research field.

REFERENCES

[1] See the Nobel Lectures: (a) K. B. Sharpless. *Angew. Chem. Int. Ed*. **2002**, *41*, 2024–2032; (b) R. Noyori. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; (c) W. S. Knowles. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998–2007.

[2] J. Halpern and B. M. Trost. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5347–5347.

[3] H. Nozaki, S. Moriuti, H. Takaya, and R. Noyori. *Tetrahedron Lett.* **1966**, *7*, 5239–5244.

[4] (a) B. List. *Chem. Rev.* **2007**, *107*, 5413–5415; (b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308.

[5] P. A. Wender. *Chem. Rev.* **1996**, *96*, 1–2.

[6] R. Noyori. *Nat. Chem.* **2009**, *1*, 5–6.

[7] B. M. Trost. *Science* **1991**, *254*, 1471–1477.

[8] R. A. Sheldon. *Green Chem.* **2007**, *9*, 1273–1283.

[9] P. Anastas and N. Eghbali. *Chem. Soc. Rev.* **2010**, *39*, 301–312.

[10] For reviews, see: (a) J. Wang, X. Liu, and X. Feng. *Chem. Rev.* **2011**, *111*, 6947–6983; (b) S. Kobayashi, Y. Mori, J. S. Fossey, and M. M. Salter. *Chem. Rev.* **2011**, *111*, 2626–2704; (c) P. Merino, E. Marqué-López, T. Tejero, and R. P. Herrera. *Tetrahedron* **2009**, *65*, 1219–1234; (d) D. Enders and J. P. Shilvock. *Chem. Soc. Rev.* **2000**, *29*, 359–373.

[11] A. Strecker. *Ann. Chem. Pharm.* **1850**, *75*, 27–45.

[12] M. S. Iyer, K. M. Gigstad, N. D. Namdev, and M. Lipton. *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911.

[13] I. S. Young and P. S. Baran. *Nat. Chem.* **2009**, *1*, 193–205.

[14] (a) P. Kraft, J. A. Bajgrowicz, C. Denis, and G. Fráter. *Angew. Chem. Int. Ed.* **2000**, *39*, 2980–3010; (b) C. Chapuis. *Helv. Chim. Acta.* **2012**, *95*, 1479–1511.

[15] D. A. Dobbs, K. P. M. Vanhessche, E. B. V. Rautenstrauch, J.-Y. Lenoir, J.-P. Genêt, J. Wiles, and S. H. Bergens. *Angew. Chem. Int. Ed.* **2000**, *39*, 1992–1995.

[16] (a) C. Fehr, J. Galindo, O. Etter, and E. Ohleyer. *Chimia* **1999**, *53*, 376; (b) C. Fehr, J. Galindo. *Angew. Chem. Int. Ed.* **2000**, *39*, 569; *Angew. Chem.* **2000**, *112*, 581.

[17] N. Krause, S. Ebert, and A. Haubrich. *Liebigs Ann. Chem.* **1997**, 2409–2418.

[18] (a) J. T. Mohr, M. R. Krout, and B. M. Stoltz. *Nature* **2008**, *455*, 323–332; (b) H.-U. Blaser, *Chem. Commun*. **2003**, 293–296.

[19] (a) T. Bui, S. Syed, and C. F. Barbas III. *J. Am. Chem. Soc.* **2009**, *131*, 8758–8759; For the simultaneously independent work realized by chiral Lewis acid catalysis: (b) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, and M. Shibasaki, *J. Am. Chem. Soc*. **2009**, *131*, 9168–9169.

[20] For a discussion, see: (a) F. Zhou, Y.-L. Liu, and J. Zhou. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407; (b) M. Ding, F. Zhou, Y.-L. Liu, C.-H. Wang, X.-L. Zhao, and J. Zhou, *Chem. Sci.* **2011**, *2*, 2035–2039.

[21] Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, and M. Sodeoka. *J. Am. Chem. Soc*. **2005**, *127*, 10164–10165.

[22] B. M. Trost and Y. Zhang. *Chem. Eur. J.* **2011**, *17*, 2916–2922.

[23] S. EI-Fayyoumy, M. H. Todd, and C. J. Richards. *Beilstein, J. Org. Chem*. **2009**. doi:10.3762/bjoc.5.67

[24] H.-U. Blaser. *Adv. Synth. Catal.* **2002**, *344*, 17–31.

[25] H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, and R. Noyori. *Angew. Chem. Int. Ed.* **1998**, *37*, 1703–1707.

[26] T. Katsuki and K. B. Sharpless. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

[27] (a) Z. G. Hajos and D. R. Parrish. *Germany Patent DE* 21022623, **1971**; (b) U. Eder, G. R. Sauer, and R. Wiechert. *Germany Patent DE* 2014757, **1971**; (c) U. Eder, G. Sauer, and R. Wiechert. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497; (d) Z. G. Hajos and D. R. Parrish. *J. Org. Chem.* **1974**, *39*, 1615–1621.

[28] (a) X. Xiao, Y. Xie, C. Su, M. Liu, and Y. Shi. *J. Am. Chem. Soc.* **2011**, *133*, 12914–12917; (b) X. Xiao, M. Liu, C. Rong, F. Xue, S. Li, Y. Xie, and Y. Shi. *Org. Lett.* **2012**, *14*, 5270–5273.

[29] E. Nakamura and K. Sato. *NatureMater.* **2011**, *10*, 158–161.

[30] (a) G. Bredig and W. S. Fiske. *Biochem. Z.* **1912**, 7; (b) H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22.

[31] U.-H. Dolling, P. Davis, and E. J. J. Grabowski. *J. Am. Chem. Soc.* **1984**, *106*, 446–447.

[32] D. Yang, Y. C. Yip, M. W. Tang, M. K. Wong, J. H. Zheng, and K. K. Cheung. *J. Am. Chem. Soc.* **1996**, *118*, 491–492.

[33] Y. Tu, Z. Wang, and Y. Shi. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807.

[34] S. E. Denmark, Z. Wu, C. Crudden, and H. Matsuhashi. *J. Org. Chem.* **1997**, *62*, 8288–8289.

[35] M. S. Sigman and E. N. Jacobsen. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.

[36] E. J. Corey and M. J. Grogan. *Org. Lett.* **1999**, *1*, 157–160.

[37] S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann and E. M. Ruel. *J. Am. Chem. Soc.* **1998**, *120*, 1629–1630.

[38] C. H. Heathcock. In *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming, C. H. Heathcock, Eds.; Pergamon: Oxford, **1991**, Vol. 2, pp. 133–179.

[39] (a) D. A. Evans, J. V. Nelson and T. Taber. In *Topics in Stereochemistry*; John Wiley & Sons: New York, **1982**, Vol. 13, pp. 1–115; (b) D. A. Evans, E. Vogel, and J. V. Nelson. *J. Am. Chem. Soc.* **1979**, *101*, 6120–6213.

[40] (a) C. H. Heathcock. *Asymmetric Synthesis*; J. D. Morrion, Ed.; Academic Press: New York, **1984**, Vol. 3, part B, p. 111; (b) W. A. Kleschick, C. T. Buse, and C. H. Heathcock. *J. Am. Chem. Soc.* **1977**, *99*, 247–248.

[41] (a) S. Masamune, S. Ali, D. L. Snitman, and D. S. Garvey. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557–558; (b) S. Masamune, W. Choy, F. A. J. Kerdesky, and B. Imperiali. *J. Am. Chem. Soc.* **1981**, *103*, 1566–1568.

[42] T. Mukaiyama. *Aldrichimica Acta.* **1996**, *29*, 59–76.

[43] (a) S. Kobayashi and T. Mukaiyama. *Chem. Lett.* **1989**, *18*, 297–300; (b) T. Mukaiyama, H. Uchiro, and S. Kobayashi. *Chem. Lett.* **1989**, *18*, 1757–1760; (c) S. Kobayashi, H. Uchiro, Y. Fujishita, I. Shiina, and T. Mukaiyama. *J. Am. Chem. Soc.* **1991**, *113*, 4247–4252.

[44] K. Furuta, T. Maruyama, and H. Yamamoto. *J. Am. Chem. Soc.* **1991**, *113*, 1041–1042.

[45] (a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, and M. Shibasaki. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871–1873; (b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, and M. Shibasaki. *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178.

[46] S. Mukherjee, J. W. Yang, S. Hoffmann, and B. List. *Chem. Rev.* **2007**, *107*, 5471–5569.

[47] B. List, R. A. Lerner, and C. F. Barbas III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

[48] A. B. Northrup and D. W. C. MacMillan. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.

[49] V. Nair, A. T. Biju, S. C. Mathew, and B. P. Babu. *Chem. Asian J.* **2008**, *3*, 810–820.

[50] (a) C. Gennari, L. Colombo, and G. Bertolini. *J. Am. Chem. Soc.* **1986**, *108*, 6394–6395; (b) D. A. Evans, T. C. Britton, R. L. Dorow, and J. F. Dellaria. *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397; (c) L. A. Trimble and J. C. Vederas. *J. Am. Chem. Soc.* **1986**, *108*, 6397–6399; (d) W. Oppolzer and R. Moretti. *Helv. Chim. Acta.* **1986**, *69*, 1923–1926.

[51] D. A. Evans and S. G. Nelson. *J. Am. Chem. Soc.* **1997**, *119*, 6452–6453.

[52] D. A. Evans and D. S. Johnson. *Org. Lett.* **1999**, *1*, 595–598.

[53] (a) B. List. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657; (b) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, and K. A. Jørgensen. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790–1793.

[54] For a review: L.-W. Xu, J. Luo, and Y. Lu. *Chem. Commun.* **2009**, 1807–1821.

[55] T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, and Y.-C. Chen. *Org. Lett*. **2007**, *9*, 3671–3674.

[56] For reviews, see: (a) H. B. Kagan and O. Riant. *Chem. Rev.* **1992**, *92*, 1007–1019; (b) A. Togni and L. M. Venanzi. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497–526; (c) U. Pindur, G. Lutz, and C. Otto. *Chem. Rev.* **1993**, *93*, 741–761; (d) L. Deloux, and M. Srebnik. *Chem. Rev.* **1993**, *93*, 763–784.

[57] Y. Hayashi, J. J. Rohde, and E. J. Corey. *J. Am. Chem. Soc.* **1996**, *118*, 5502–5503.

[58] D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy, and K. R. Campos. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.

[59] A. Erkkilä, I. Majander, and P. M. Pihko. *Chem. Rev.* **2007**, *107*, 5416–5470.

[60] K. A. Ahrendt, C. J. Borths, and D. W. C. MacMillan. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

[61] A. B. Northrup and D. W. C. MacMillan. *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460.

[62] E. M. Vogl, H. Groger, and M. Shibasaki. *Angew. Chem. Int. Ed.* **1999**, *38*, 1570–1577.

[63] J.-H. Xie, X.-Y. Liu, J.-B. Xie, L.-X. Wang, and Q.-L. Zhou. *Angew. Chem. Int. Ed.* **2011**, *50*, 7329–7332.

[64] H.-U. Blaser, H. P. Buser, K. Loers, R. Hanreich, H. P. Jalett, E. Jelsch, B. Pugin, H. D. Schneider, F. Spindler, and A. Wagmann. *Chimia* **1999**, *53*, 275–280.

[65] J. Staunton and K. J. Weissman. *Nat. Prod. Rep.* **2001**, *18*, 380–416.

[66] X. Gao, S. K. Woo, and M. J. Krische. *J. Am. Chem. Soc.* **2013**, *135*, 4223–4226.

[67] For a recent review: L. Marchetti and M. Levine. *ACS Catal.* **2011**, *1*, 1090–1118.

[68] (a) K. A. Brown and J. Kraut. *Faraday Discuss.* **1992**, *93*, 217–224; (b) V. I. Polshakov. *Russ. Chem. Bull.* **2001**, *50*, 1733–1751; (c) A. E. Allen, and D. W. C. MacMillan. *Chem. Sci.* **2012**, *3*, 633–658.

[69] L. Bernardi, M. Fochi, M. C. Franchini, and A. Ricci. *Org. Biomol. Chem.* **2012**, *10*, 2911–2922.

[70] (a) Y.-M. Chook, H. Ke, and W. H. Lipscomb. *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 8600–8603; (b) Y.-M. Chook, J. V. Gray, H. Ke, and W. H. Lipscomb. *J. Mol. Biol.* **1994**, *240*, 476–500; (c) A. Y. Lee, P. A. Karplus, B. Ganem, and J. Clardy. *J. Am. Chem. Soc.* **1995**, *117*, 3627–3628.

[71] (a) T. Ema, J. Kobayashi, S. Maeno, T. Sakai, and M. Utaka. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 443–453; (b) T. Ema, T. Fujii, M. Ozaki, T. Korenaga, and T. Sakai. *Chem. Commun.* **2005**, 4650–4651.

[72] M. Svedendahl, K. Hult, and P. Berglund. *J. Am. Chem. Soc.* **2005**, *127*, 17988–17989.

[73] For a review: C. Belle and J.-L. Pierre. *Eur. J. Inorg. Chem.* **2003**, 4137–4146.

[74] (a) D. E. Wilcox, A. G. Porras, Y. T. Hwang, K. Lerch, M. E. Winkler, and E. I. Solomon. *J. Am. Chem. Soc.* **1985**, *107*, 4015–4027; (b) E. I. Solomon, U. M. Sundaram, and T.

E. Machonkin. *Chem. Rev.* **1996**, *96*, 2563–2605; (c) C. Gerdemann, C. Eicken, and B. Krebs. *Acc. Chem. Res.* **2002**, *35*, 183–191.

[75] T. Klabunde, N. Sträter, R. Fröhlich, H. Witzel, and B. Krebs. *J. Mol. Biol.* **1996**, *259*, 737–748.

[76] J. A. Tainer, E. D. Getzoff, J. S. Richardson, and D. C. Richardson. *Nature* **1983**, *306*, 284–287.

[77] T. D. Machajewski and C.-H. Wong. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1374.

[78] T. P. Yoon and E. N. Jacobsen. *Science* **2003**, *299*, 1691–1693.