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Multistep One-Pot Reactions Combining Biocatalysts and Chemical Catalysts for Asymmetric Synthesis

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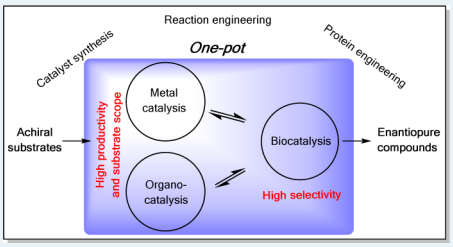
ABSTRACT: In a continuous effort to emulate the efficiency of biosynthetic pathways, considerable progress has been made in developing one-pot chemoenzymatic processes that take full advantage of the chemo-, regio-, and stereoselectivity of biocatalysts and the productivity of chemical catalysts. Over the last 20 years, research in this area has provided us with proof of concept examples in which chemical and biological transformations occur in one vessel, sequentially or concurrently. These transformations typically access products with high enantiopurity and chemical diversity. In this perspective, we present some of the most successful reports in this field.



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INTRODUCTION

Catalytic asymmetric synthesis is built on three pillars: metal catalysis, organocatalysis, and biocatalysis. Over the years, catalysts of these three classes have enabled groundbreaking chemical transformations. The application of chemocatalysis to the manufacturing of chemicals is widespread, and biocatalysis is increasingly being used industrially;[1] however, the conditions under which these catalytic operations are developed are generally fine-tuned for individual reactions. In a multistep synthesis, each reaction typically occurs in a separate vessel. After most steps, a purification step is conducted, which results in high process costs, incurs yield losses, and generates large amounts of waste. Therefore, the need to reduce waste and processing costs has turned the attention of chemists toward developing tandem processes that combine catalytic transformations within or across the three disciplines of asymmetric synthesis.[2]

Multistep one-pot processes, so-called tandem processes, have the potential to impact the manufacturing of fine chemicals and pharmaceutical intermediates.[3] In catalytic asymmetric synthesis, they offer an attractive approach to improve the overall efficiency of chemical transformations, starting from simple and readily available achiral substrates to access chiral compounds with high enantio- and regioselectivity. Compared with stepwise synthesis, the combination of multiple catalytic reactions into one synthetic operation reduces the number of purification steps, thus contributing to an improved process economy as well as to more sustainable synthetic routes. In addition, multistep one-pot reactions can improve stereochemical control and substrate scope and can suppress side reactions. Lastly, the cooperative effect between multiple catalysts can enhance reactivity and selectivity by allowing equilibrium reactions to proceed to nearly full conversion.

An important requirement for an efficient one-pot tandem process is the compatibility of the individual reaction steps with one another. Finding conditions to enable all reactions to proceed efficiently and catalysts that are compatible with one another while retaining the selectivity obtained from individual reactions are two main limitations that have generally hampered the development of the field. To overcome these difficulties, several strategies have been developed, including the physical separation of the catalysts using two phases or encapsulation techniques, the sequential addition of catalysts and reactants, or the use of compatible catalysts. As a result, numerous examples of one-pot processes have been reported.

However, most tandem processes developed to date are based on chemocatalytic multistep reactions, multienzyme reactions, and pure biotechnological processes, such as fermentations. One-pot reactions involving biocatalysts and chemical catalysts are more challenging because of incompatibilities stemming mainly from the radically different environments in which catalysts from these two disciplines usually operate as well as mutual inactivation that often occurs when chemical catalysts and enzymes are combined in one vessel.

From synthetic and industrial points of view, the combination of chemical catalysts and biocatalysts in one pot in ways to access highly enantiopure chiral compounds would be valuable. Chemical catalysis and biocatalysis are often considered two complementary fields. In many cases, catalysts from these fields effect the same reactions but with different rates, scopes, and selectivities; however, in some cases, they

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catalyze completely different reactions, the counterparts of which cannot be found in the other field. In addition, catalysts from each of these fields present certain advantages and limitations. For example, organometallic catalysts can react with a wide substrate scope and with high productivity. However, chiral metal complexes tend to be sensitive to species with coordinating ability in the reaction system and generally cannot achieve the very high enantio- and regioselectivities required for fine chemical synthesis without the help of directing and protecting groups. Biocatalysts operate under environmentally friendly conditions and offer exquisite regio- and enantioselectivities that may not be achievable by chemical catalysts in many cases, but they generally exhibit low stability in organic solvents and high temperatures as well as low to no activity toward many nonnative substrates. Nevertheless, advances in protein engineering continue to provide us with options to tailor the performance of a biocatalyst to improve its affinity for unnatural substrates of industrial or pharmaceutical relevance as well as to enhance its stability toward organic solvents.[4]

Since the pioneering works of Williams,[5] Backväll,[6] and Kim[7] combining metal catalysts with lipases and serine proteases for the dynamic kinetic resolution of alcohols and amines, more effort is now being spent bridging the gap between chemical catalysts and biocatalysts to reap the benefits of both catalytic systems in one-pot syntheses. As a result, more and more one-pot chemoenzymatic reactions are emerging. In this perspective, we summarize the recent achievements of one-pot chemoenzymatic reactions. A brief presentation and summary of dynamic kinetic resolutions and other applications using lipases and metal racemization catalysts will be discussed. Finally, we will review recent developments of one-pot chemoenzymatic reactions (sequential and concurrent) that have demonstrated a potential to push back the boundaries of this field.

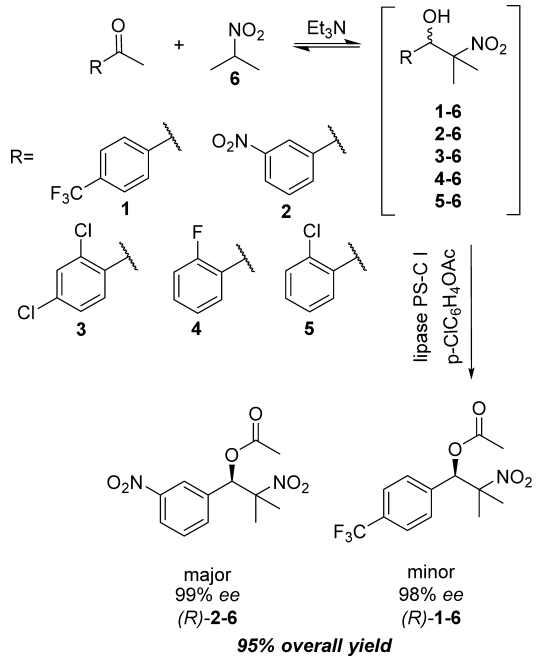
DYNAMIC KINETIC RESOLUTION

Dynamic kinetic resolutions (DKRs) catalyzed by metal racemization complexes and lipases or proteases are now well-established methods for the preparation of single enantiomers from racemates.[8] Enzymatic kinetic resolutions are highly selective, but their main drawback is that a maximum yield of only 50% can be obtained for the desired enantiomer. Integration of a racemization catalyst in the system to continuously replenish the depleted enantiomer can theoretically drive the resolution up to 100% yield for the enantiomer of interest, thereby reducing or eliminating further separation steps. For kinetic resolutions, lipases (specifically, the immobilized *Candida antarctica* lipase B (CALB)[8d]) have been the enzymes of choice because of their robustness and activity in organic solvents at temperatures up to 100 °C. Since the native CALB is *R*-selective, to obtain the *S* enantiomer, *C. antarctica* lipase A (CALA), an engineered *S*-selective lipase,[9] or a serine protease such as subtilisin[7,10] have all been used.

For the racemization reaction, different transition metal complexes have found success, depending on the substrate scope and compatibility with the enzyme. The majority of racemization catalysts suitable for the DKR of alcohols are ruthenium complexes, some of which are found to be active at room temperature, which can be paired with thermolabile enzymes.[11] Rhodium, palladium, aluminum, and vanadium catalysts have also been active, but effective for only limited substrates.[11] In particular, the readily available trimethylaluminum catalyzes the dynamic kinetic resolution of secondary alcohols at room temperature.[12] The racemization of amines is more challenging and, therefore, less developed. Palladium complexes have been found to be the most active for primary amine racemization.[11] Ruthenium complexes, Raney Ni, and iridium[13] complexes are now being integrated into the DKR of amines. For example, racemization of aliphatic amines was achieved at lower temperatures when the reactions were run with Raney Ni than when run with other complexes.[14] Recently, the DKR of secondary amines has been achieved using a dimeric Cp* Ir complex and a lipase from *C. rugosa*.[15] DKRs have now been applied to prepare various enantiopure secondary alcohols, including diols and functionalized alcohols, as well as primary and secondary amines and amino acids. Excellent reviews of these advances have appeared elsewhere.[16]

As a further expansion of their applicability, DKRs with lipases are now being applied in the synthesis of drugs and pharmaceuticals.[13,17] In addition, lipases are being used to resolve dynamic combinatorial libraries (DCLs), as exemplified by the intriguing work of Ramström and co-workers.[18] In their work, a dynamic set of 10 nitroaldol adducts was generated by a reversible C−C-bond-forming Henry reaction of 5 aldehydes with 2-nitropropane (Scheme 1). When the nitroaldol equilibrium mixture was added in one pot with the lipase PS-C I from *Pseudomonas cepacia*, two products from the DCL were resolved with an overall yield of 95% in 14 days. Since the two products resolved were among the lowest present in the DCL equilibrium, the nitroaldol−lipase dynamic combinatorial resolution process not only resolved the specific *β*-nitroalcohol derivatives but also led to a high yield of selective derivatives of the Henry reaction products.

Scheme 1. Direct Asymmetric Lipase-Mediated Screening of a Dynamic Nitroaldol Library



Moberg and co-workers reported a minor enantiomer recycling process effected by a chiral Ti Lewis acid metal catalyst, a Lewis base organocatalyst, and a lipase working in concert in a biphasic system (Scheme 2).[19] The chiral Ti Lewis acid (*S*,*S*)-[(salen)Ti-*μ*(m-O)]2 and the Lewis base (4-dimethylaminopyridine or 1,8-diazabicyclo[5.4.0]undec-7-ene)

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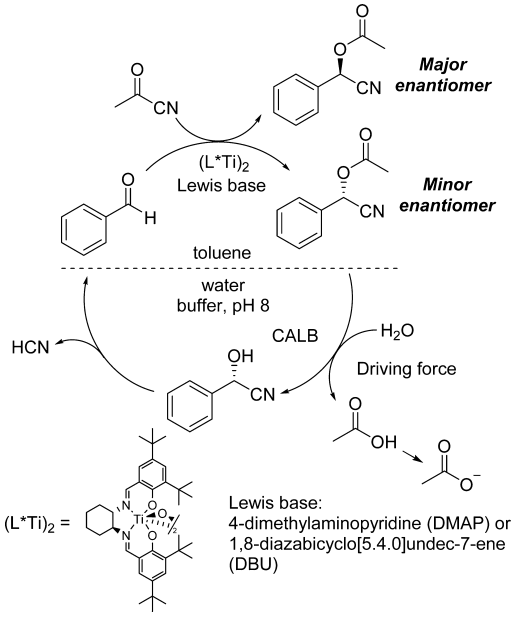
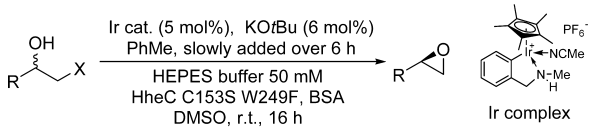
Scheme 2. Minor Enantiomer Recycling: Metal Catalyst, Organocatalyst, and Biocatalyst Working in Tandem



perform the acylcyanation of an aldehyde in toluene to produce O-acylated cyanohydrins in moderate ee (~62% for the *R* enantiomer). The minor *S* enantiomer is recycled through hydrolysis by CALB in water to regenerate the aldehyde, thus allowing the system to obtain O-acylated cyanohydrins in close to perfect enantioselectivities and in high yields. Interestingly, although a combination of a (*S*,*S*)-salen Ti Lewis acid and CALB provides the products with *R* absolute configuration, the opposite enantiomer is obtained from the (*R*,*R*)-salen Ti complex and *C. rugosa* lipase. This is the first report in which catalysts from all three classes have been used cooperatively.

DKRs have started to be extended beyond lipases and proteases to include other less stable enzymes. Although lipase-based DKR has been developed for a wide variety of substrates, few DKRs of *β*-haloalcohols have been reported. To achieve a DKR of *β*-alcohols to enantiopure terminal epoxides, Janssen, Feringa, and de Vries combined a haloalkane dehalogenase (HheC) with an iridium complex (Scheme 3).[20] HheC catalyzed the kinetic resolution of chloroalcohols through a ring-closing reaction that transformed the *R* enantiomer of the substrate to the corresponding epoxide. In parallel, the *S* enantiomer is racemized by an iridium complex. This approach

Scheme 3. DKR of *β*-Haloalcohols Catalyzed by the Combination of an Iridacycle and a Haloalkane Dehalogenase

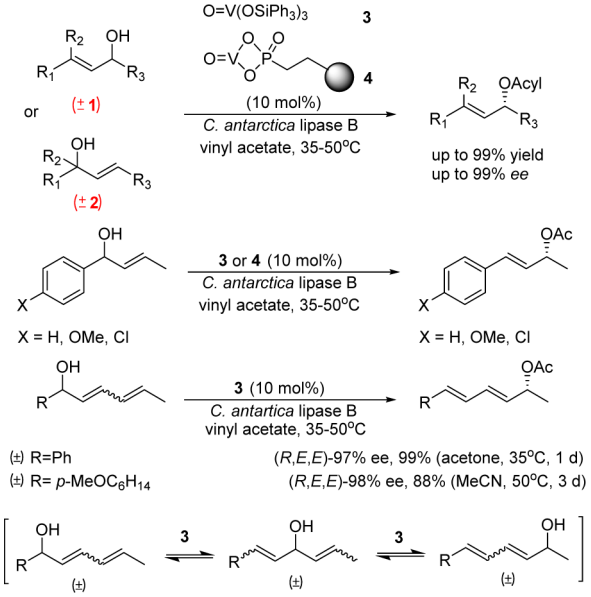


R	X	conv (%)	*ee* (%)
C_6H_5	Cl	90	98
4-NO_2-C_6H_4	Br	86	90
3-NO_2-C_6H_4	Br	79	52
4-CN-C_6H_4	Br	89	86

resulted in moderate to high yields and moderate to high ee values for the preparation of several styrene oxide derivatives.

Lipases are inherently able to discriminate between stereoisomers; discrimination between a mixture of regio- and stereoisomers, however, is more difficult to achieve. Akai and co-workers showed that the combination of a vanadium-oxophosphate complex and CALB formed optically active allylic esters by a regio- and enantioconvergent transformation of racemic allyl alcohols (Scheme 4).[21] In their system, the

Scheme 4. One-Pot Synthesis of Optically Active Allyl Esters via Lipase–Vanadium Tandem Catalysis



vanadium complexes catalyzed the continuous racemization of the alcohols along with the 1,3-transposition of the hydroxyl group, which created all possible regio-constitutional and stereoisomers. The lipase CALB, in turn, effected the chemo- and enantioselective esterification of only one of the allylic alcohols to achieve the DKR. Several (*R*)-phenyl allyl acetate derivatives were prepared in >90% ee, with yields ranging from 70 to 99%. Remarkably, this one-pot racemization was able to produce pure (*R*)-dienyl acetates in high yields and ee's, which required the lipase to discriminate among at least nine regio- and stereoisomers resulting from a 1,3,5-transposition.

■ ONE-POT CASCADE CHEMOENZYMATIC REACTIONS

With the exception of immobilized lipases and serine proteases, a large fraction of biocatalysts are incompatible or poorly stable in pure organic solvents, at high temperatures, or in the presence of small molecule catalysts, salts, and catalytic components. As a result, the integration of biocatalysts in one-pot reactions with chemical catalysts remains undeveloped. Many chemoenzymatic processes reported in the literature occur in separate vessels as distinct steps, and a purification step is included after each reaction to remove unreacted substrates, side products, and catalysts that could be incompatible with the subsequent steps.[22] In recent years, one-pot cascade chemoenzymatic transformations have been published in which the separation of reactants, catalysts, or intermediates prior to the subsequent reaction steps is not required. In certain cases, strong evidence of the coexistence of chemical catalysts and

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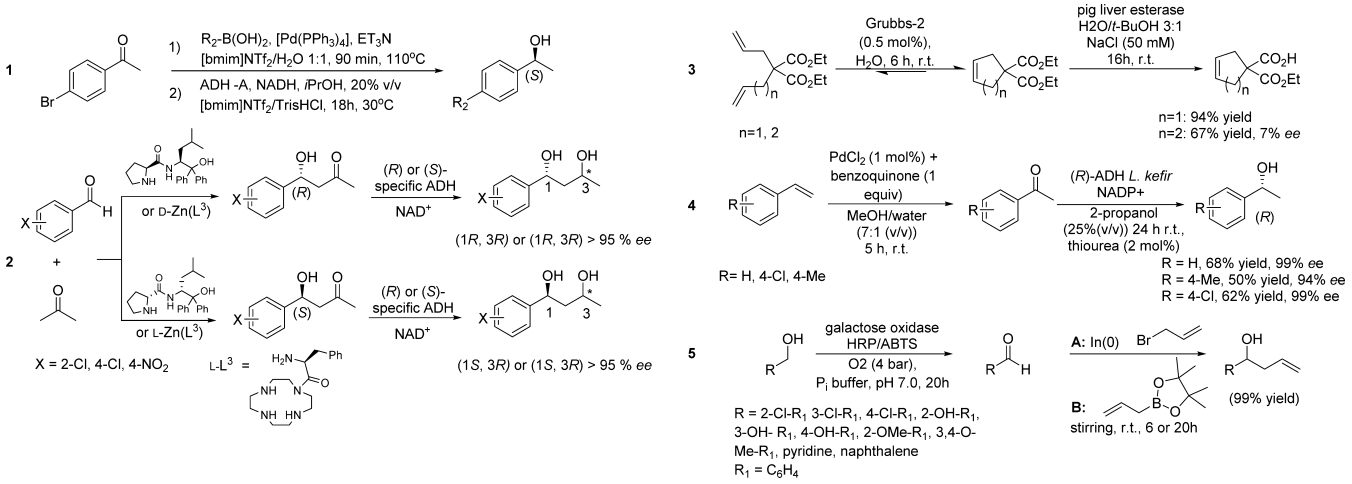
Scheme 5. Examples of One-Pot Cascade Chemoenzymatic Reactions



enzymes is presented; however, different reaction conditions required for the catalytic and enzymatic steps, a disparity in reaction rates, as well as the enzyme's substrate selectivity restrict these systems to being sequential instead of concurrent.

Schmitzer and Gröger developed a two-step chemoenzymatic cascade approach for the preparation of chiral biaryl alcohols by combining a Pd-catalyzed Suzuki cross-coupling reaction with a stereospecific enzymatic reduction.[23] In this sequential process, $Pd(PPh_3)Cl_2$ catalyzed the cross-coupling between phenylboronic acid and aryl ketones at 70 °C in water in 99% yield. At the end of the first reaction, without isolation of the cross-coupling product, conditions were adjusted for the stereospecific reduction of the biaryl ketone by an *S* specific alcohol dehydrogenase (ADH) from *Rhodoccocus* sp. Interestingly, studies of the effects of the Suzuki coupling components on ADH activity revealed that the Pd catalyst had no inhibitory effects, even at concentrations near the complex's solubility limit, whereas free phosphane, an additive in the coupling reaction, inhibited ADH at high concentrations. By removing this additive from the system, overall yields of 91% were obtained for the preparation of three (*S*)-biaryl alcohols in >99% ee. The substrate scope of this reaction was later expanded by using a two-phase ionic liquid/buffer system in which the Suzuki coupling reaction occurred in the ionic liquid phase (Scheme 5, entry 1).[23b]

Alcohol dehydrogenases also have been successfully combined with proline organocatalysts[24] or Zn-catalysts[25] to obtain enantioenriched 1,3-diols in one-pot (Scheme 5 entry 2). In particular, Aoki and co-workers tested several conditions for the aldol reaction between acetone and benzaldehyde using proline or chiral Zn^{2+} complexes of L- and D-phenylalanyl-pendant[12]aneN4 (L-ZnL3 and D-ZnL3) in aqueous solution to obtain both *R* and *S* aldol addition products in high ee. In addition, several oxireductases were screened for the asymmetric reduction of *β*-hydroxyketones to yield chiral diols. When the two catalyst systems were combined in a cascade one-pot reaction, using the right combination of a chiral organocatalyst or Zn- complex with an *S*- or *R*-specific ADH could yield each of the four chiral diol stereoisomers in moderate to quantitative yields and >95% *ee*.

Similarly, an olefin metathesis catalyst was combined with a pig liver esterase in a sequential one-pot fashion for the synthesis of cyclic malonic acid monoesters, as reported by Groger and co-workers.[26] A ruthenium carbene complex catalyzed the ring-closing metathesis of diallyl malonate or diethyl 2-allyl-2-(but-3-en-1-yl)malonate on top of buffer. At the end of the catalytic reaction, pig liver esterase was added, and after optimization of the cosolvent volume ratio, the cyclic malonic monoesters were obtained in 67−95% yields (Scheme 5, entry 3). Although the metathesis catalyst did not have any negative impact on the enzyme and the pig liver esterase reacted selectively with the ring-closed intermediate over the ring-open starting material, this process was sequential. Reaction times for the metathesis and hydrolysis were 6 h and >50 h, respectively.

A one-pot reaction for the preparation of chiral secondary alcohols through a direct asymmetric transformation of vinylarenes was recently reported by Gröger et al.[27] In this system, a Pd-catalyzed Wacker-Tsuji reaction first transformed the vinylarene to a ketone; subsequently, an alcohol dehydrogenase catalyzed an asymmetric reduction to afford (*R*)-secondary alcohols with >99% ee (Scheme 5, entry 4). To obtain a compatible reaction system, ligands such as 2,2-bipyridine, thiourea, and EDTA were introduced in catalytic amounts to remove Pd species before the enzymatic reduction because the Pd species were found to interfere with this step. By this approach, styrene, *p*-chlorostyrene, and *p*-methylstyrene were transformed to their respective (*R*)-phenylethan-1-ol derivatives with moderate yields and >90% enantioselectivity. Most importantly, this approach could be amenable to a concurrent process if a thermotolerant alcohol dehydrogenase that operates in organic solvents could be introduced.

One feature of a one-pot tandem reaction is the in situ generation and direct conversion of compounds with functional groups that undergo side reactions if allowed to remain in solution. For example, aldehydes, which participate in various reactions of industrial importance, such as nucleophilic additions, condensations, reductions, and oxidations, are sometimes unstable or readily react to unwanted products. Ways to generate aldehydes in situ and to convert them directly to other valuable and more stable functionalities are advantageous.

To address this issue, Faber and co-workers developed a one-pot procedure for the chemoenzymatic synthesis of homoallylic alcohols (Scheme 5, entry 5).[28] Because the conditions of the allylation reaction were found to completely inactivate the enzyme, the reaction was developed as a two-step process. *Escherichia coli* whole cells expressing a galactose oxidase

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converted aryl and diaryl alcohols to their corresponding aldehydes, which were subsequently coupled to an allyl moiety derived from the combination of indium and allyl bromide or from an allylboronic ester in a noncatalytic fashion.

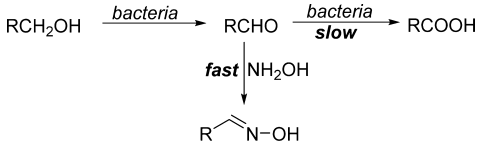
ONE-POT CONCURRENT CHEMOENZYMATIC TRANSFORMATIONS

As highlighted in the previous section, one of the major factors that has prevented the successful integration of chemical catalysis and biocatalysis in concurrent tandem processes is the distinct reaction conditions used for the different classes of catalysts. This includes solvent choice and temperature as well as mutual inactivation of the two catalysts, which often occurs.

Reports of one-pot, concurrent chemoenzymatic reactions have only just started to emerge. So far, these processes have been limited to a relatively small number of chemical reactions that can occur at mild temperatures, as well as a small number of biocatalysts that are compatible with conditions required for the chemical catalyst to operate satisfactorily.

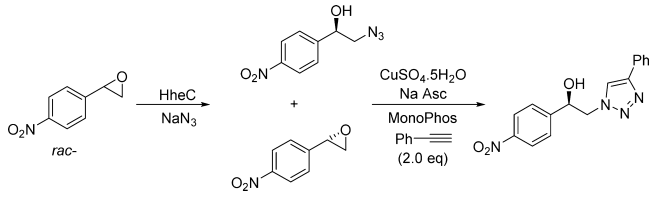
Molinari et al. developed a synthetic method for the one-pot preparation of aldoximes, which have wide applications in medicine, industry, and analytical and synthetic chemistry.[29] They combined the enzymatic oxidation of primary alcohols using different acetic acid bacteria with an in situ condensation of the resultant aldehydes with hydroxylamine. In the absence of hydroxylamine, the oxidation of primary alcohols catalyzed by membrane-bound alcohol and aldehyde dehydrogenases of acetic acid bacteria generally leads to carboxylic acids through the further oxidation of aldehydes. However, since the rate of aldehyde oxidation was slower than the condensation reaction between the intermediate aldehydes and hydroxylamine, aldoximes were preferentially formed. Although high concentrations of hydroxylamine were found to inhibit the whole cell transformations, several aldoximes were obtained in moderate to high yields (50−90%) from phenyl-alcohol derivatives (Scheme 6).

Scheme 6. One-Pot Chemoenzymatic Synthesis of Aldoximes from Primary Alcohols



The copper-catalyzed 1,3-dipolar cycloaddition of azides and alkynes (CuAAC) to form 1,4-disubstituted triazoles is a common reaction used to form covalent connections between building blocks containing various functional groups. As a result, it has seen applications in various areas, including drug discovery and polymer chemistry as well as medicinal and biological sciences.[30] The bioorthogonality of this reaction is especially suited for one-pot procedures with enzymes. Recently, efforts have been directed at engineering one-pot transformations involving CuAAC with biocatalysts. Feringa and co-workers demonstrated that an azidolysis of aromatic epoxides by HheC could be combined in one pot with a subsequent CuCAAC reaction with phenylacetylene (Scheme 7).[31] To afford the highest yields, the enzyme HheC was added in two portions, and the starting substrate concentration was kept below 5 mM to prevent enzyme−substrate inhibition. The

Scheme 7. One-Pot Tandem Azidolysis−CuAAC



substrate scope of this reaction encompassed only styrene and *p*-nitrostyrene.

Another area in which combinations of metal catalyst and enzymes have been successful is in the chemical and electrochemical regeneration of cofactors used in redox enzymatic reactions. The in situ regeneration of expensive cofactors in enzymatic redox reactions is absolutely necessary for preparative scale transformations. Enzymes that regenerate cofactors are abundant in nature and have been readily used for large-scale cofactor regeneration. However, the applicability of these enzymes may be limited under certain process conditions because of their strict preference for a specific cofactor (NADPH, NADH, or flavin, for example) and low stability in organic solvents and at high temperatures. A few thermostable dehydrogenases have been identified,[32] and protein engineering has partly addressed problems of stability and cofactor preference of a few of these enzymes.[33] Although enzymatic cofactor regeneration remains the method of choice for preparative-scale redox reactions,[34] several less expensive, more versatile mediators, mainly organometallic complexes which regenerate cofactors and their analogues, have been extensively studied.[35]

Among the complexes that can catalyze chemical and electrochemical regeneration, pentamethylcyclopentadienyl rhodium bipyridine ($[Cp^*Rh(bpy)(H_2O)]^{2+}$) is particularly attractive because it is active on several cofactors and their analogues and is stable over a very broad temperature and pH ranges. Therefore, this electrocatalyst represents an alternative to enzymatic regeneration systems under certain process conditions.[36] However, mutual inactivation is still an issue when the Rh-based complex is combined with alcohol dehydrogenases.[37]

The interaction between ($[Cp^*Rh(bpy)(H_2O)]^{2+}$) and the alcohol dehydrogenase from *Thermus* sp. ATN was investigated in detail.[38] Isolated amino acids, primarily cysteine, histidine, tryptophan, and methionine were found to exert an inhibiting effect on $[Cp^*Rh(bpy)(H_2O)]^{2+}$, suggesting that these amino acids are likely to be the coordinating residues within the alcohol dehydrogenase[39] which results in the mutual inactivation of both catalysts. To prevent direct contact between the enzyme and the Rh mediator, a polymer-bound Rh complex was synthesized, and physical separation between the two catalytic centers was implemented. This engineered system could achieve a yield of 90% of (*R*)-phenyl-ethanol via ketone reduction.

Although mutual inactivation occurs in the presence of the Rh mediator, an iron(III) porphyrin was found to be fully compatible with enzymes for the regeneration of $NADP^+$.[40] After testing several water-soluble iron porphyrins, Fe(III) meso-tetrakis(4-sulfonatophenyl)porphyrin was found to efficiently oxidize NAD(P)H while reducing molecular oxygen to water. By combining this porphyrin with a glucose dehydrogenase from *Bacillus subtilis* or an alcohol dehydrogenase, efficient

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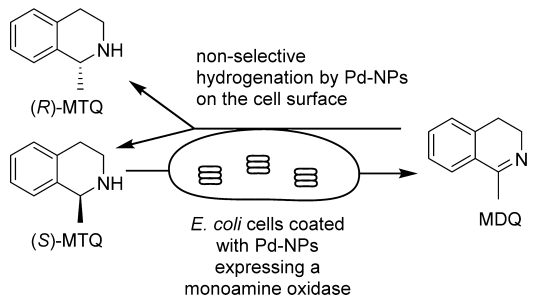
enzymatic oxidations of monosaccharides and cyclooctanol were achieved, respectively.

NOVEL WAYS TO COMBINE ENZYMES AND CATALYSTS IN ONE-POT CONCURRENT SYSTEMS

Mutual inactivation has not been investigated in-depth because it occurs on a case-by case basis. The interactions between chemical catalysts and enzymes differ, depending on the characteristics of the two catalysts as well as the reaction being catalyzed. Therefore, a general model or prediction for mutual inactivation is far from being realized. However, new strategies are being developed to circumvent mutual inactivation between metal catalysts and biocatalysts. These new approaches hold tremendous promise for future chemo-enzymatic applications because they describe potentially general ways for carrying out classic organic reactions in the presence of biocatalysts.

One approach to enable cascade or concurrent chemo-enzymatic reactions to occur without mutual inactivation is to compartmentalize the catalytic systems, shielding the catalytic centers from one another. Ways to achieve such compartmentalization traditionally included biphasic reaction conditions, site isolation, membrane filtration,[41] or enzyme immobilization within solid supports. Alternatively, the use of whole cells could provide a natural protection for biocatalysts. A method that combined a nonselective palladium hydrogenation catalyst with an enantioselective bio-oxidation system to produce enantiopure cyclic secondary amines was recently reported.[42] Aerobic cultures of *E. coli*, overproducing a recombinant monoamine oxidase possessing high enantioselectivity toward chiral amines were coated with nanoscale Pd(0) precipitated via a bioreduction reaction on the cell membrane.[43] Using this biometallic whole-cell catalyst, the enzyme oxidizes only the *S* enantiomer of racemic 1-methyltetrahydroisoquinoline (MTQ) to form 1-methyl-3,4-dihydroisoquinoline (MDQ), which is then reduced back to the racemic amine by a nonselective Pd/H_2 reduction (Scheme 8). Since hydrogen and air could not be

Scheme 8. Deracemization of a Cyclic Secondary Amine



pressurized in the reaction vessel at the same time, the deracemization required five cycles of air alternated with five cycles of hydrogen to catalyze the oxidation and reduction steps, respectively, and achieve the (*R*)-MTQ in 96% ee. This work is especially important because few methods are reported for the preparation of enantiopure secondary amines, in contrast to primary amines, which can be obtained through a metal−lipase DKR system.

Another interesting approach to enable chemo-enzymatic reactions in one pot would be to create "hybrid" catalysts bearing two or more orthogonal but complementary catalytic activities. Conceptually, this draws similarities to biometallic whole cell catalysts, but expands the chemical scope. Palomo and co-workers recently hinted at such a possibility.[44] They described the synthesis of novel enzyme−metal nanoparticles (NPs) nanobiohybrids in which metal nanoparticles were generated in situ from an aqueous noble metal salt solution. These CALB-metalNPs hybrid catalysts were tested for their respective orthogonal reactions separately and in tandem. CALB-PdNPs were capable of catalyzing Heck coupling, Suzuki coupling, and nitroarene reduction (metal catalysis) reactions as well as a lipase transesterification (biocatalysis). Interestingly, an amine DKR was also achieved in high yields and >99% ee.

Incorporating metal catalysts inside a protein host has long been an intense area of research for the creation of artificial metalloenzymes.[45] Artificial metalloenzymes give access to both the reactivity and substrate scope of metal complexes and the regio- and stereoselectivity afforded by the second coordination sphere of a protein host. Hollmann, Turner, and Ward recently applied this approach to develop synthetic cascades by combining an artificial transfer hydrogenase (ATHase), created by incorporating a biotinylated [Cp*Ir(Biot-*p*-L)Cl] complex within streptavidin (Sav), with several biocatalysts.[46] Whereas mutual inactivation occurred when the free Ir complex and the biocatalysts were combined, the encapsulated metal complex enabled one-pot concurrent reactions with three different enzymes. First, a double stereoselective amine racemization was achieved in combination with a monoamine oxidase to form enantiopure cyclic secondary amines. Second, the formation of L-pipecolic acid from L-lysine was achieved by combining the ATHase with L-amino acid oxidase and a D-amino acid oxidase to enrich the L-pipecolic acid enantiomer. Third, the regeneration of NADH by the ATHase to promote a monooxygenase-catalyzed oxyfunctionalization reaction was also described. These reactions all reached 80% to near quantitative yields, which indicated that the Sav-Ir complex was fully compatible with the enzymatic reactions.

Similar to the incorporation of transition metal complexes within streptavidin, the use of supramolecular host−guest complexes allows synthetic catalysts to work collaboratively with enzymes. First, supramolecular assemblies have been shown to stabilize reactive metal species and increase their lifetime.[47] Second, water-soluble supramolecular host−guest assemblies can pull hydrophobic organometallic complexes into an aqueous solution, therefore permitting certain reactions traditionally performed in organic solvents to occur in water.[47,48] Lastly, the supramolecular host−guest assembly prevents diffusion of the transition metal complex in the solution, thereby averting its direct interaction with proteins.[47,49]

Using a supramolecular approach, Bergman, Raymond, Toste, and co-workers demonstrated tandem reactions that employed esterases, lipases, or alcohol dehydrogenases and Au(I) or Ru(II) complexes encapsulated in a Ga_4L_6 tetrahedral supramolecular cluster.[50] First, lipases and esterases were combined with a Au(I)−Ga_4L_6 host−guest complex for a cascade lipase hydrolysis, followed by a hydroalkoxylation of allenes (Scheme 9). Second, they achieved a Ru(II)-mediated olefin isomerization of 2-propen-1-ol to give propanal, followed by reduction to propanol via ADH catalysis. The yields obtained from the one-pot reaction were identical to those obtained in the case of sequential reactions.

CONCLUSION

Strategies that enable one-pot tandem chemoenzymatic reactions are still in their infancy. The development of this

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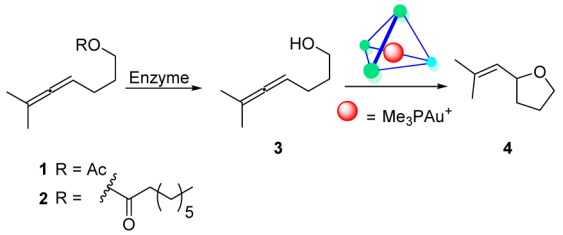
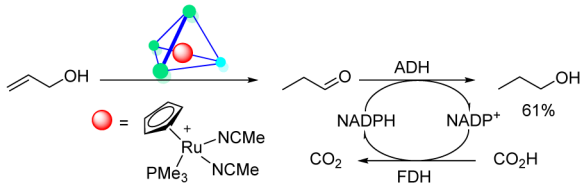
Scheme 9. Examples for Metal Catalysts Encapsulated within Supramolecular Complex in Tandem with Biocatalysts



Substrate	Product	Enzyme	[Au] cat	Product ratio (1 or 2:3:4)
1	3	Rabbit liver esterase	Me_3PAu^+ Me_3PAuCl	(0:0:100) (14:24:62)
2	3	Mucor mieihi lipase	Me_3PAu^+ Me_3PAuCl	(0:0:100) (15:0:65)



field has been slow, mainly because of the often incompatible conditions required for chemocatalyzed and enzyme-catalyzed transformations. Tandem processes, so far, generally consist of two to three catalytic reactions, even when catalysts from the same category are combined. The limited number of steps is in sharp contrast to natural biosynthetic pathways in which tens of enzymes work in harmony to achieve very complex transformations. Since the metal–lipase DKR, several well-characterized chemical transformations have been combined with enzymes to achieve either sequential or concurrent one-pot processes. However, the variety of enzymes that has been integrated, as well as the number of chemical transformations that can be coupled in tandem, has been limited. To expand the synthetic capabilities of one-pot chemoenzymatic reactions, contributions from several interdependent research areas are necessary (e.g., but not limited to protein engineering, chemical catalyst synthesis, supramolecular assembly, and artificial metalloenzymes).

Protein engineering strategies to improve enzyme stability in organic solvents or in harsh conditions (e.g., high temperatures) is important for the integration of chemical and biological transformations in one pot. Many milestones have been achieved in the engineering of enzymes to operate in organic solvents[51] and high temperatures via directed evolution[4,52] and enzyme immobilization techniques.[51a,53] Similarly, in recent years, synthetic chemistry has been focusing on developing catalysts that can be effective at mild conditions and in aqueous environments. Current advances in this area have provided us with many examples of water-soluble metal complexes that catalyze a variety of reactions (e.g., olefin metathesis,[54] Pd-catalyzed hydrogenation,[55] and C–C coupling reactions in aqueous environments[56]).

Supramolecular approaches are beginning to provide potentially general approaches to create synthetic cascades involving transition-metals catalysts and enzymes. One current limitation of the supramolecular incorporation of transition metal complexes is that complexes bearing a net positive charge are more easily incorporated within the water-soluble supramolecular ligands than neutral complexes.[47,49] Further engineering needs to be performed to increase the scope of metal complexes that can be introduced. In addition, development of supramolecular scaffolds that mimic enzyme active sites to mediate substrate recognition via preferential binding will be advantageous to maintain reaction selectivity in cases when several metal catalysts are present.[57]

Artificial metalloenzymes, in particular, those based on the biotin–avidin technology, are starting to be well-studied for a variety of chemical transformations in water,[45e,f] including C–H activation, Diels–Alder reactions, hydrogenations, and oxidations. Further developments of artificial metalloenzymes are needed to improve the productivity and stability of the catalyst employed.

In summary, we envision that with advances in all these research areas in parallel, concurrent tandem chemoenzymatic processes can be orchestrated to mimic biosynthetic pathways, in which many enzyme-catalyzed processes are able to function simultaneously, resulting in the most complex reactions known.

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Notes

The authors declare no competing financial interest.

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