Review Article

The Upside of Downsizing: Asymmetric Trifunctional Organocatalysts as Small Enzyme Mimics for Cooperative Enhancement of Both Rate and Enantioselectivity With Regulation

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ABSTRACT

Small molecule organic catalysts (organocatalysts) are widely used in asymmetric catalysis and synthesis. Compared to their enzymatic and transition-metal counterparts, organocatalysts have advantages in catalytic scope and efficiency but are more limited in proficiency. Chiral trifunctional organocatalysts, in which multiple catalytic motifs act cooperatively on a chiral scaffold, are an emerging class of organocatalysts with improved proficiency. Cooperativity design that enables both enantioselectivity and rate enhancement is essential to developing future generations of organocatalysts in biomimetic asymmetric catalysis. Chirality 25:675–683, 2013. © 2013 Wiley Periodicals, Inc.

KEY WORDS: multifunctional organocatalysts; catalytic proficiency; REAP factor; enantioselective activation; proton transfer; organocatalysis regulation; catalytic assembly

INTRODUCTION

Enzymes, transition-metals, and small organic molecules are the three main classes of molecular catalysts for asymmetric reactions. What defines an “ideal” catalysis? High enantioselectivity and yields; fast rates; low loading; ambient and “green” reaction conditions, preferably in water or recyclable solvents; and facile catalyst recovery. These are essential criteria on which most can agree. It is also possible that catalyst renewability may become a requirement in the near future. Furthermore, good reaction scope with rapid and cost-effective customization is paramount to the applicability of any catalyst at the preparative scale.

Enzymes generally meet most, if not all, of the above criteria, and have served as inspirations for designed systems, particularly in terms of catalytic proficiency. Designed, smaller organic molecules, or organocatalysts, with catalytic proficiency, may offer advantages over enzymes or transition metals. By tracing the developmental steps of asymmetric organocatalysis, and examining some of its current challenges, the questions on cooperativity design for enzyme-mimicking proficiency are discussed here.

ASYMMETRIC ORGANOCATALYSIS: FROM CONCEPT TO PRACTICE

The earliest demonstration of a small organic catalyst possibly came in the mid 19th century when Justus von Liebig used aqueous acetaldehyde to facilitate formation of oxamide from dicyan (eq. 1).

\[
\text{NC} - \text{CN} + \text{CH}_2\text{CHO} \rightarrow \text{H}_2\text{O}, \text{r.t.} \quad \text{H}_2\text{N} - \text{CH} = \text{O} - \text{NH}_2
\]

Liebig, 1852

Emil Knoevenagel later in 1896 referred to the amines in his aldol condensation of β-ketoesters or malonates with aldehydes or ketones as “Kontaktsubstanz,” a species actively involved in the reaction but not consumed (eq. 2).

\[
\text{MeO}_2\text{C} - \text{CO}_2\text{Me} + \text{PhCHO} \rightarrow \text{H}_2\text{O} \quad \text{MeO}_2\text{C} - \text{CO}_2\text{Me}
\]

Knoevenagel, 1896

In 1900, the formal term coining of an organic catalyst appeared in an article by Wilhelm Ostwald, who discussed some of the catalytic nature of enzymes (“die Fermente”), along two other types of catalysts, organic catalysts (“organische Katalysatoren”) and inorganic catalysts (“anorganische Katalysatoren”). The conception of catalysis by small organic molecules, inorganic molecules, or enzymes alike was already evident.

The field of “organocatalysis” continued on, without much fanfare. In 1913, Bredig and Fiske’s hydrocyanation reaction catalyzed by quinine or quinidine exhibited slight asymmetric induction (eq. 3).

\[
\text{CH}_3\text{CHO} + \text{H}_2\text{SO}_4, \text{HCN} \rightarrow \text{OH} \quad \text{OH} \rightarrow \text{CO}_2\text{H}
\]

Bredig, 1913

Langenbeck, after Dakin’s report of amino acids as catalysts, further popularized the term “organische Katalysatoren” in aminocatalysis with bifunctional catalysts such as N-methylglycine. In 1960 Pracejus reported the first significantly enantioselective conversion of methyl phenyl ketene to its propionate ester catalyzed by benzoylequinine with 76% ee (eq. 4).

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The asymmetric induction capacity of organic catalysts, however, was not definitively recognized until 1970, when the Hajos-Parrish-Eder-Sauer-Wiechert reaction used (S)-proline to catalyze an intramolecular aldol reaction with 92% ee (eq. 5).9–12

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In those years asymmetric organocatalysis did not experience rapid growth, possibly due to its somewhat inconsistent proficiency in asymmetric induction. In the 80s and 90s, asymmetric organic catalysts with high ee's continued to appear. Dolling et al.'s17 cinconinium bromide as a phase-transfer catalyst furnished alkylated indanones with up to 95% yield, 92% ee, at 10 mol% loading (eq. 7).

The Yang and Shi groups used chiral ketones in epoxidation with up to 95% ee (eqs. 8, 9), which scope-wise improved from Juliá's poly-alanine catalyst ("synthetic enzymes").18–20 However, the 300–1000 mol% loading levels may contest their role as catalysts but rather auxiliaries in trans.

The Lipton, Jacobsen, and Corey groups reported hydrocyanation of imines catalyzed by a cyclic dipeptide, a thiourea, and a guanidine, respectively (eqs. 10, 11, and 12)

with enantioselectivity up to 99% at 2–10 mol% loading.21–23 Concurrently, the Miller group reported an N-alkylimidazole tripeptide for catalyzing kinetic resolution of alcohols at 84% ee (eq. 13).24

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Hatakeyama in 1999 catalyzed a Baylis–Hillman reaction with a chiral quinidine at 99% ee and 10 mol% loading (eq. 14).25 While the banner of “asymmetric organocatalysis” was absent, these examples demonstrated clearly the validity of this catalytic approach.

Meanwhile in the parallel world of biocatalysis, investigations of enzyme catalytic theories and mechanisms, coupled with technical development for rapid and diversified protein synthesis and manipulation, gave birth to catalytic antibodies in the 80s.27 In particular, a catalytic antibody catalyzed an intermolecular aldol reaction between a ketone and aldehyde via an enamine intermediate.28 Five years later, in 2000, (S)-proline was used by List et al.29 to mimic this enamine activation mechanism as a “microaldolase” for direct intermolecular aldol reactions with up to 96% ee (eq. 15).

Concurrently, the first imidazolidinone catalyzed Diels–Alder reaction between enals and dienes via a proposed iminium intermediate was reported by the McMillan group with up to 96% ee (eq. 16).30

Crystal clear, finally, was the idea that asymmetric organocatalysis could be a general approach beyond just “sporadic” examples. In a

Scheme 2. An example of cooperative catalysis. a) Povarov reactions between N-aryl imines and electron rich olefins. b) A Povarov reaction catalyzed by HOTf and 1. c) An energy diagram of the cooperative catalysis by HOTf and 1.

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little over a decade, this field is in full swing, with extensive applications in complex synthesis. A century and a half after Liebig’s observation, organocatalysts are now accepted alternatives to enzyme and transition-metal catalysts in addressing demanding synthetic needs.

THE REAP FACTOR: REQUIREMENTS FOR REAPING THE BENEFIT

In hindsight, one might attempt to identify the ingredients necessary for maturation of a catalytic approach. Four characteristics are proposed here to be important in catalysis: rationale, efficiency, adaptability, and proficiency (the REAP factor). The catalytic rationale relies on mechanistic investigation and underpins the ability to discover new catalysis. Catalytic efficiency refers to the overall cost–benefit ratio of the process in practical terms. Catalytic adaptability requires the catalyst design to be modular such that customization can proceed expediently. Catalyst proficiency, defined by the intrinsic potency of a catalyst, refers to the level of rate enhancement and asymmetric induction. Organic catalysts, while in use the earliest, did not begin to establish their role under these criteria until much later. Enzyme catalysis meets the criteria of rationale, efficiency, and proficiency, but its adaptability can be limited, although directed evolution may offer viable alternatives. Transition-metal catalysts are often highly proficient, with low catalyst loading, easily adaptable by sampling metal centers and ligands, and mechanistically articulated to guide the catalyst design. However, the use of precious or toxic metal centers with potentially prohibitive cost from purification may reduce the catalytic efficiency.

For asymmetric organocatalysis, the issues of rationale, adaptability, and efficiency have been extensively addressed. For example, computational, kinetic, spectroscopic, spectrometric, and structural investigations have collectively explained proline catalysis in terms of the geometry of the enamine intermediate (Scheme 1), and other modes of organoactivation have been elucidated. High efficiency has been demonstrated by a solid-phase bound chiral thiourea that maintained 98% yield, 93% ee after 10 recycles in gram-scale hydrocyanation of imines. Multifunctional peptide catalysts, synthesized modularly, can be adapted for a wide range of reactions by an iterative process of screening and selection. On catalytic proficiency (high rate, high enantioselectivity, and low loading), asymmetric organocatalysis perhaps is still in its infancy, with limited examples. Rawal and co-workers used TADDOL to catalyze a day-long hetero-Diels–Alder reaction with only one enantiomeric product detected (eq. 17), albeit at 20 mol% loading. Wang et al. reported, for a Michael–Michael cascade process, a thiourea catalyst at 2 mol% loading with 97% ee and 86% yield in 15 hours at room temperature (eq. 18).

Most recently, Maruoka’s group reported asymmetric conjugate additions catalyzed by chiral phosphonium salts with up to 91% ee at 0.1 mol% loading (eq. 19).

Scheme 3. Multivalent catalysts and multicatalysis. a) An example of bifunctional catalysis with multivalent H-bonding sites. b) An example of multicatalysis acting in different stages of a cascade hydride transfer–α-C fluorination reaction.
Nonetheless, mild, fast, and highly enantioselective reactions at low catalyst loading are rare in organocatalysis. Addressing this proficiency issue will not only firmly secure asymmetric organocatalysis as the third pillar of modern catalysis but also answer some fundamental questions in catalytic hypotheses.

**CATALYTIC PROFICIENCY AND COOPERATIVITY: TWO SIDES OF THE SAME COIN?**

Catalytic proficiency for enzymes is defined by the intrinsic catalytic rate, often for only one enantiomeric product, and the binding affinity of the substrate.\(^5\) For example, triosephosphate isomerase catalyzes the transfer of a proton in D-glyceraldehyde-3-phosphate to form dihydroxyacetone phosphate from the si face with 10\(^{10}\)-fold rate acceleration (eq. 20).\(^5\)

Within the transition state binding theory, the rate enhancement and enantioselectivity in enzyme catalysis is inherently coupled as its active site has evolved to activate only the cognate reaction pathway. Enormous catalytic proficiency is harnessed by cooperatively organizing mild acids or bases in the active site, as best exemplified by orotidylate decarboxylase with 10\(^{17}\)-fold rate enhancement.\(^6\) In enantioselective organocatalysis, rate-coupled asymmetric induction remains a challenge, when the pathways to different enantiomeric outcomes are often differentiated by steric factors. Lowering reaction temperatures may maximize the steric bias but this also reduces reaction rates. The catalyst loading can be high unless the rate-limiting step is also effectively catalyzed. To improve on proficiency, one approach is to combine multiple activation motifs cooperatively. An example of acid activated organocatalysis in the Povarov reaction demonstrates a general strategy for cooperative catalysis.\(^6\)

The Povarov reaction refers to the cycloaddition of N-aryl imines and electron-rich olefins to form tetrahydroquinolines, which can be catalyzed by HOTf via imine protonation (Scheme 2a). Chiral additives, containing multidentate H-bond donors (urea, thiourea, and sulfonamide) and steric-directing groups, can bind to both the conjugate base of HOTf and the protonated imine in a particular orientation, thus enabling enantiofacial selectivity (up to 99% ee).

However, such cooperativity in enantioselectivity is not always mirrored in rate enhancement. The organocatalysis of this Povarov reaction by the strong Brønsted acid HOTf alone, which is not enantioselective, is faster without the weaker, chiral Brønsted acid additive such as 1 (Scheme 2b). The addition of 1 presents the reaction with two concurrent catalytic directions, A (racemic catalysis without 1) and B (enantioselective catalysis with 1) (Scheme 2c). The rate-limiting step in A is about 5-fold faster than that of B (\(\Delta G_{\text{a}} < \Delta G_{\text{B}}\)) at the expense of the rate. Also, the reaction temperature is lowered substantially to \(-50^\circ\text{C}\) with prolonged reaction time. As shown by this example, enantioselectivity may be associated with kinetic deceleration, in the absence of cooperative kinetic factors.

**Scheme 4.** A trifunctional organocatalyst for an enantioselective 1,3-dipolar cycloaddition. a) A trifunctional organocatalyst for asymmetric 1,3-dipolar cycloaddition. b) Enantioselective organocatalysis of 1,3-dipolar cycloaddition between enones and azomethine imines.

**Scheme 5.** A trifunctional organocatalyst for a transesterification reaction. a) A trifunctional mimic of the catalytic triad of esterases. b) An organocatalytic transesterification reaction with large rate enhancement.

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activation. The joint rise of enantioselectivity and rate in asymmetric organocatalysis remains a challenge in its cooperativity design.

TRIFUNCTIONAL ORGANOCATALYSIS: TOWARD COOPERATIVITY IN ASYMMETRIC INDUCTION AND RATE ENHANCEMENT

Trifunctional organocatalysis is conferred by synergistic action of three different catalytic motifs. The definition of a catalytic motif follows the List formalism, in which acid or base activation can be enabled by Lewis acids, Lewis bases, Brønsted acids, and Brønsted bases.63 Trifunctional organocatalysis is differentiated here from "multifunctional organocatalysis," a term used loosely without clear distinction between catalytic motifs and catalytic valencies. For example, an organocatalyst, with one Brønsted base, such as a tertiary amine, and several weak Brønsted acids as H-bond donors, will be considered here as a bifunctional catalyst, while it may be considered a "multifunctional" organocatalyst by others simply due to the multivalency of the interaction between the H-bond donors and acceptors (Scheme 3a).64

Unlike its predecessors, such as monofunctional or bifunctional organocatalysts, trifunctional organocatalysts operate in a more complex catalytic landscape where it is in competition with the monofunctional or bifunctional background pathways. If the synergy, or positive cooperativity, of its three catalytic motifs is low, then trifunctional catalysis may not outcompete in rate in the lower-order catalysis and result in low enantioselectivity, low rate, or both.

Such design difficulty is, however, offset by the new opportunities in trifunctional organocatalysis whereby mild motifs with cooperativity may be effectively assembled without the need of strong modes of activation. In general, such asymmetric cooperative catalysis with mild motifs aims to selectively accelerate one enantiomeric pathway over the background or noncooperative pathways, as typically seen in enzyme active sites. More proficient catalysis may be possible with enantioselective activation compared to the approach of rate deceleration for enantio-bias, in which case the rate is reduced for all pathways and the least suppressed pathway delivers the observed enantioselectivity.

Thus far, three trifunctional organocatalytic systems, with distinct functional assignment of each catalytic motif and demonstration of trifunctional cooperativity, are known and discussed in chronological order. The first trifunctional catalyst, reported in 2007 by Chen et al.,67 is a cinchona alkaloid derivative, 2, with a primary amine, a tertiary amine, and a phenol (Scheme 4a). An achiral acid is added as a cofactor. This catalytic system promotes an enantioselective 1,3-dipolar cycloaddition reaction between cyclic enones and azomethine imines in excellent yields (67–99%) and enantioselectivity (86–95% ee) (Scheme 4b). The primary amine acts as a Lewis base and forms an imine with the enone substrate, which is further protonated by the acid additive to form a ketonium ion pair as the activated dipolarophile. The phenol acts as a Brønsted acid and binds to the azomethine carbonyl for activation and orientating the dipole. The tertiary amine acts as a Brønsted base to form an ion pair with the acid additive for instigating the enantiofacial bias. As a bifunctional control, catalyst 2a without the phenol group was tested and found to be inferior in both rate and enantioselectivity. The mechanistic details of this system are not fully disclosed, the positive cooperativity of the Lewis base, Brønsted acid, and Brønsted base is likely the basis for
the observed joint rise in enantioselectivity and rate under near-ambient reaction conditions. The enantioselectivity of the reaction is also preserved at 2 mol% catalyst loading.

The second case is the Sakai-Emä catalyst 3, reported in 2008 for a transesterification reaction between vinyl acetates and alcohols (Scheme 5). The trifunctional organocatalyst contains a general base (pyridine), a nucleophile (alcohol), and a Bronsted acid (thiourea). The three catalytic motifs are mimics of the catalytic triad in the active site of serine hydrolase. In the enzymatic site, a general base (histidine) activates the hydroxy nucleophile from a serine residue for attacking the acyl carbonyl of the substrate. The oxyanion intermediate from this nucleophlic acyl addition is then stabilized by an “oxyanion hole”—a network of H-bond donors formed by peptide backbone amide hydrogens. Such a Bronsted base–Lewis base–Bronsted acid catalytic triad is recapitulated in the Sakai-Emä catalyst to achieve astonishing rate enhancement of 10^5-fold compared to the uncatalyzed rate. More important, the bifunctional controls of the trifunctional catalyst, 3a–3c, whereby only two of the three catalytic motifs are present, show only background reaction rates and demonstrate convincingly that the positive cooperativity requires all three motifs for rate enhancement. While it is a racemic catalyst and still far from reaching the proficiency of its natural counterparts, the Sakai-Emä catalyst 3 represents a seminal case toward mechanism-based, positive cooperativity design with rigorous controls for biomimetic organocatalysis of impressive rates.

The third case is the Liu–Garnier trifunctional catalytic system, represented by 4, that we reported in 2009 for an enantioselective aza-Morita–Baylis–Hillman (MBH) reaction (Scheme 6). The MBH or aza-MBH reaction is a three-step reaction sequence with complex mechanisms (Scheme 6a). The reaction is initiated by a Lewis base, usually an amine or phosphine, that undergoes a Michael addition to form a zwitterionic phosphonium enolate from the starting enone. The electrophile, either an aldehyde or imine, then undergoes an aldol-like reaction with the enolate, where a carbon–carbon bond is formed. Both of these two steps are reversible, and the reaction is not productive until the third, proton transfer–elimination (PTE) step releases the catalyst and forms the final MBH product. Because the final product contains a protic source, the MBH reaction is rate-limited by the PTE step only during early conversion but later switches to the aldol step with the MBH product itself catalyzing the PTE step.

This complexity and autocatalysis inherent in the MBH mechanism, where the stereogenecity is controlled by both thermodynamic and kinetic factors in all three steps, has made its catalysis difficult, with often low rate, capricious substrate scope, and inconsistent enantioselectivities. We focused our attention on activating selectively only one PTE pathway in a model aza-MBH reaction between methyl vinyl ketones (MVK) and N-tosyl imines by cooperative trifunctional organocatalysis. The prototype system 4 contains a phosphine, an α-amino group, and a phenol (Scheme 6b). An external, achiral carboxylic acid is also required as a catalytic cofactor. Three bifunctional controls, 4a–4c, were tested to elucidate the role of each catalytic motif and demonstrated that all three are required for the observed positive cooperativity. The phosphine acts as the Lewis base to initiate the Michael step. The α-amino group is required for enabling the activation of the external acid, and the phenol is essential for enhancing the rate and enantioselectivity. Under ambient reaction conditions, both electron-rich and electron-poor N-tosyl imines reacted with MVK in good rates (3–24 h for 86–94% isolated yields) and enantioselectivity (up to 92% ee), catalyzed by 4 containing the Lewis base–Bronsted acid–Bronsted base triad in the presence of benzoic acid. A second-generation catalyst, 5, in some cases produced near quantitative conversion at 10 mol% loading in 15 min at ambient temperature with good enantioselectivity.

An intriguing feature is highlighted by the regulatory function of the external acid additive (Scheme 6c, arrow to the left). In the absence of the external benzoic acid additive, the catalysis by the chiral catalyst 4 is not only slow but also non-enantioselective. However, in the presence of benzoic acid, enantioselective catalysis is enabled with a joint rise of rate and enantioselectivity (up to 94% ee), which suggests that the cooperativity between 4 and benzoic acid is essential to this enantioselective activation. Further structure-based mechanistic analysis is ongoing in order to unravel the molecular basis to this regulated catalytic assembly.

Two of the aforementioned enantioselective trifunctional organocatalytic systems, 2 and 4, do not have enzymatic counterparts in nature, although the engineered candidates are emerging. The 1,3-dipolar reactions and aza-MBH reactions they catalyze represent some of the most facile and enantioselective versions for these reactions by organocatalysts. All three trifunctional systems are most active at ambient or near-ambient temperatures, which is advantageous over approaches that require lower temperatures for improving enantioselectivity. For our catalyst 4, lowering temperature in fact only impedes the rate, with little improvement in enantioselectivity. At this stage, none of these systems has been adapted for catalysis at the preparative scale under greener conditions. Nevertheless, these systems stand to encourage further development in higher-order organocatalysis toward enzyme-like efficiencies under more environmentally benign conditions to promote preparative applications, particularly for reactions that do not have enzymatic versions.

**FUTURE DIRECTIONS: BIOMIMETIC ASYMMETRIC ORGANOCATALYSIS WITH REGULATION**

Enzymes remain the most proficient class of catalysts, from which a few lessons on catalyst design can be learned. As discussed above, the activation modes and motifs in enzymatic active sites are a rich source of inspiration to designed systems, and much has been developed in organocatalysis to achieve high rate and enantioselectivity under mild reaction conditions. Enzymatic catalysis, however, exhibits many more marvelous characteristics in terms of regulation and cooperativity. Enzyme catalysis can be turned on and off by cofactors, allosteres, or post-translational modifications. One enzyme can adopt multiple forms with varying substrate specificity or catalytic rate. In biosynthetic pathways, multiple enzymatic active sites are clustered to form mega-enzymes that assemble several building blocks into structurally complex natural products. Such supramolecular structures act cooperatively and perform regulated cascade catalysis in a sequence-defined manner; that is, the enzymatic assembly line not only sequesters reactivity but also orders it. Such exquisite catalytic control, with regulation, diversification, and timing, is currently unknown to designed systems.
One may argue that the conceptual foundation of asymmetric organocatalysis has always been intimately connected to that of enzymatic catalysis, starting from Ostwald’s conclusion in 1900. Following the initial examples of enamine/iminium catalysis, a few enzymatic activation modes have now been incorporated into asymmetric organocatalysts with very high enantioselectivity. The use of multiple organocatalytic pathways in one pot to convert simple building blocks into highly elaborate structures is an exciting frontier of cooperative multidentate organocatalysis that potentially may grow into mimics of biosynthetic enzyme assembly lines.

The complexity embedded in enzyme catalysis will continue to challenge the design of next-generation organocatalysts. As more and more organocatalytic systems appear, however, the questions of proficiency and cooperativity will intensify as emerging limits of this field. Much of this development will rely on rigorous characterization of organocatalytic mechanisms such that cooperativity can be approached rationally. New mimics of enzyme catalytic mechanisms should also unlock new catalytic activation modes and motifs needed to sample new catalytic space. To achieve ultimate catalytic proficiency and efficiency, regulation design is likely to be essential for developing assembled organocatalysis with complex cooperativity in the near future.

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