Spatiotemporal control for integrated catalysis

Shijie Deng,[1,#] Brandon J. Jolly,[1,#] James R. Wilkes,[2] Yu Mu,[2] Jeffery A. Byers,[2] Loi H. Do,[3] Alexander J. M. Miller,[4] Dunwei Wang,[2] Chong Liu,[1] and Paula L. Diaconescu[1]*

[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E. Young Drive East, Los Angeles, California 90095, United States

[2]Department of Chemistry, Eugene F. Merkert Chemistry Center, Boston College, 2609 Beacon Street, Chestnut Hill, Massachusetts 02467, United States

[3]Department of Chemistry, University of Houston, 4800 Calhoun Road, Houston, Texas 77004, United States

[4]Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

[#]These authors contributed equally.

*Corresponding author: pld@chem.ucla.edu

Abstract

Integrated catalysis is an emerging methodology that can streamline the multistep synthesis of complicated products in a single reaction vessel, achieving a high degree of control and reducing the waste and cost of an overall chemical process. Integrated catalysis can be defined by the use of spatial and temporal control to couple different catalytic cycles in one pot. This primer discusses commonly employed approaches and their underlying mechanisms, and elaborates on how the integration of spatially and temporally controlled catalysis in one pot can deliver the synthesis of complex products with high efficiency. We highlight recent advances, analyze current applications and limitations, and provide an outlook for the future development of integrated catalysis.

[H1] Introduction

Chemical synthesis plays a crucial role in modern technology and everyday life. From plastics to pharmaceuticals, virtually every facet of society is impacted by our ability to construct small molecules and macromolecules. A major focus in chemical research is the development of efficient methods for the production of synthetic chemicals. In 2017, the chemical industry was responsible for 10% of the total annual global energy consumption (and 28% of industrial energy consumption).[1,2] Thus, alternative approaches to chemical synthesis that minimize energy consumption and increase efficiency are needed.

The majority of commodity chemicals, pharmaceuticals and consumer materials are prepared in multistep syntheses that require catalysts to achieve high yields with selectivity toward the desired products.[3] A drawback of such methods is that they require time, energy, and exhaustive effort between reaction steps to separate and purify stable reaction intermediates. Alternative methods that enable multistep sequences would remove the need to isolate such species. A particularly attractive approach for chemical synthesis is integrated catalysis, in which multiple catalysts are carefully controlled and positioned to allow efficient multistep reaction sequences, funneling products generated by one catalyst to the next.

A combination of catalytic processes, either involving one catalyst or multiple catalysts with orthogonal reactivity, (FIG. 1a)[4] may be classified as a cascade or domino process **[G]** if only one linear reaction sequence occurs. If multiple reactions are proceeding simultaneously, then it is considered a tandem process **[G]**. Examples of integrated catalysis are often special cases of tandem catalysis, in which multiple catalysts operate through orthogonal mechanisms synergistically or can be switched on/off using external triggers. The recent literature has many excellent examples of cascade or tandem processes,[4-20] but integrated processes are rarely reported. Multiple catalytic processes operating together could be solely chemo− or bio− based, or a combination of the two. In this primer, we will focus on chemocatalytic systems.

Integrated reactions hold promise to be more efficient than an iterative process; combining spatial and temporal control avoids the need for separation and purification of intermediate steps. Furthermore, combining spatial and temporal control may also lead to the development of new chemistry and novel products. For example, a hypothetical integrated catalytic system (FIG. 1b) with spatiotemporal control can allow the efficient conversion of a starting material (gold square) to an intermediate (brown square). This intermediate can diffuse to another part of the reactor where a second catalyst, spatially separated so as not to interact with the first catalyst, reacts with and couples the intermediate with a second reactant (green square). The second catalyst may also be temporally switched to a state where it is now active for the incorporation of a third reactant (blue square). This approach could be a general strategy to synthesize complex structures that are not accessible using conventional methods, as such methods do not typically consider spatial and temporal control.

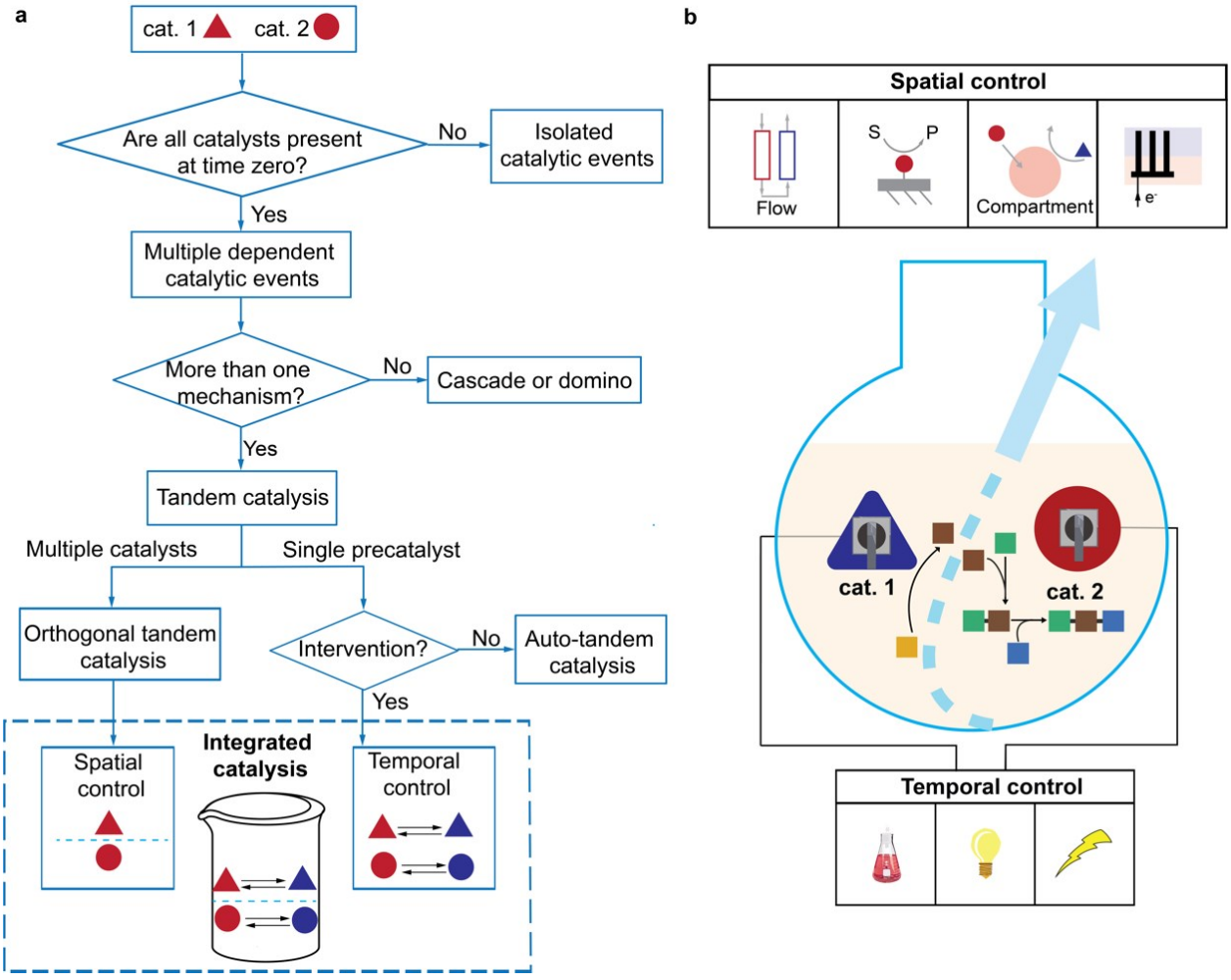


Fig. 1| Concept of integrated catalysis. a| A flowchart guide to nomenclature of different multistep one-pot catalytic processes. b| Illustration of integrated catalysis. In a hypothetical integrated catalytic system with spatiotemporal control, the starting material (gold square) is efficiently converted to an intermediate (brown square). This intermediate could then react with another catalyst that would combine the synthesized intermediate with another reactant (green square). The second catalyst can also be switched on to incorporate a third reactant (blue square). This approach can be a general strategy for synthesizing complex structures that are not available by conventional methods. Temporal control methods include external stimuli, e.g., chemical reagents, light, electron transfer, etc., whereas spatial control can be achieved by using flow chemistry, immobilization, compartmentalization, and microscopic concentration gradients.

To enable multiple catalysts to operate concurrently, issues relating to compatibility must be overcome. For example, potentially problematic catalyst-catalyst, catalyst-reactant, and catalyst-product interactions need to be addressed. To reconcile potential incompatibility, spatial and/or temporal control are required to manipulate where and when certain processes occur. Spatial control may be employed to localize and separate catalysts or entire catalytic systems from each other. This may be achieved in a number of approaches (vide infra), namely compartmentalization [G],[8,21-27] immobilization onto a

surface,[28-35] or by taking advantage of microscopic concentration gradients.[18,20,36,37] By preventing incompatible species from coming into contact with each other, efficient integrated processes may be promoted. In addition to spatial control, introducing temporal control can also alleviate compatibility concerns. If two processes compete with or hinder each other's activity, deactivating one while the other is active can help avoid incompatibility. Temporal control may be achieved using a variety of external stimuli[38-41] to switch between different states of a catalyst that have orthogonal reactivity **[G]** toward certain substrates.

In this primer, approaches to achieve spatial and temporal control in catalysis to achieve integrated catalysis are discussed. Seminal studies illustrating spatiotemporal control of catalysts will be presented to showcase their impact on some of the most challenging problems in catalysis. The development of a toolbox for integrated catalysis is also discussed, followed by limitations and suggested optimizations for this nascent field of research. Lastly, the direction in which integrated catalysis is likely to make progress in the next 5-10 years is discussed.

[H1] Experimentation

This section outlines considerations for the temporal and spatial control of a number of catalytic systems. By the use of examples, reaction processes and mechanisms are discussed, as well as considerations for each catalytic system. The typical setup for catalytic systems and design considerations for such systems are described.

[H2] Temporal control

In nature, living organisms have the ability to respond to environmental factors, causing them to behave differently or take on different forms. At the microscopic level, external stimuli regulate feedback loops and modulate enzymatic reactions within cells to effect biological changes. Taking inspiration from nature, scientists have been working on artificial catalytic systems that could be tuned reversibly by external stimuli. In such switchable systems, a catalyst could be toggled on/off or may oscillate between different catalytic states to achieve orthogonal reactivity. Depending on the application and reaction conditions, different external stimuli can be used to implement a switchable behavior. In this section, redox, chemo-, and photo-switching will be discussed, with a focus on the switching mechanisms and general catalyst design concepts. Several comprehensive reviews have been published on temporally switchable catalysis.[38,40-43]

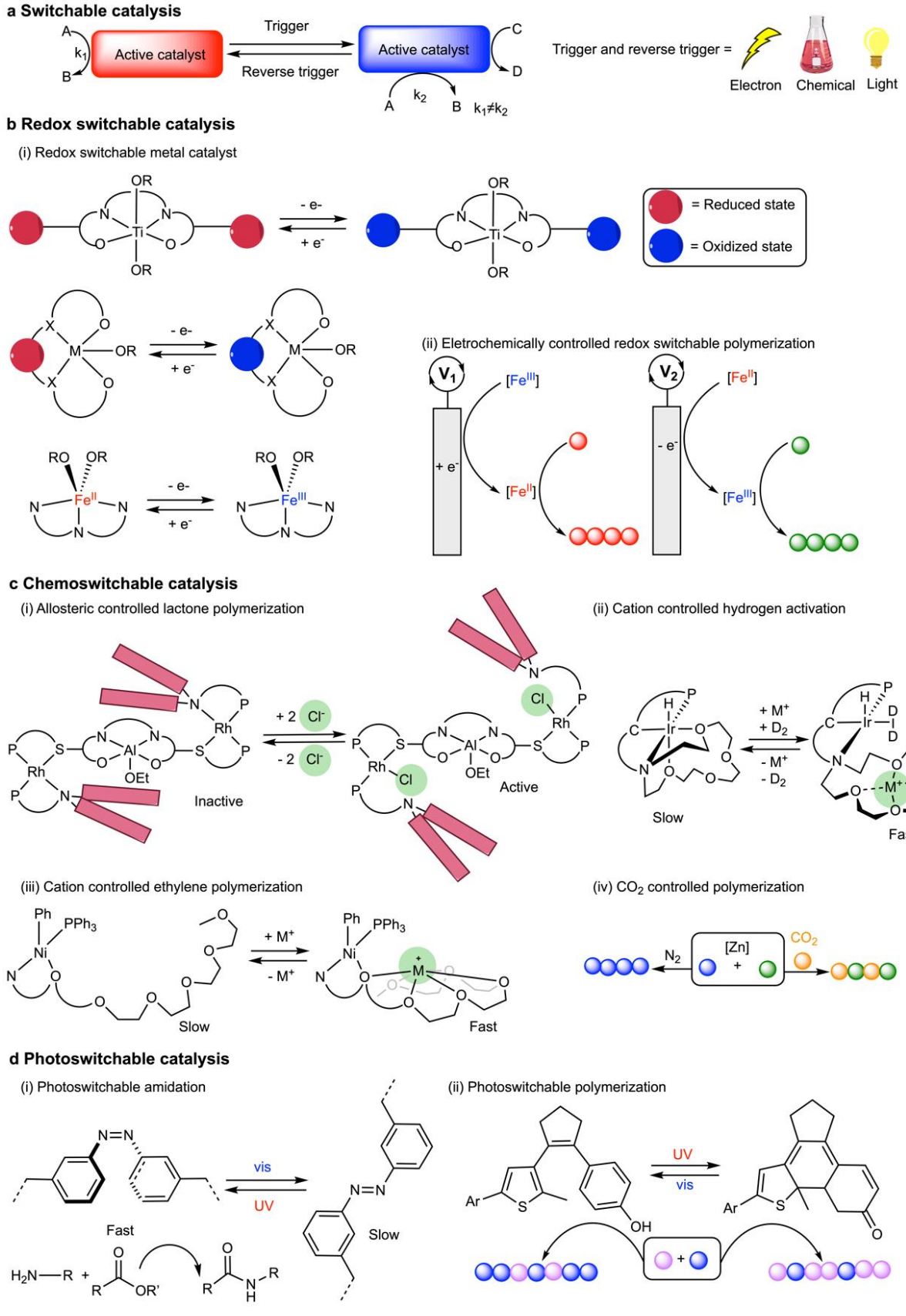

a Switchable catalysis
Active catalyst
Trigger
Reverse trigger
Active catalyst
Trigger and reverse trigger =
Electron
Chemical
Light
b Redox switchable catalysis
(i) Redox switchable metal catalyst
= Reduced state
= Oxidized state
(ii) Eletrochemically controlled redox switchable polymerization
c Chemoswitchable catalysis
(i) Allosteric controlled lactone polymerization
Inactive
Active
(ii) Cation controlled hydrogen activation
Slow
Fast
(iii) Cation controlled ethylene polymerization
Slow
Fast
(iv) CO2 controlled polymerization
d Photoswitchable catalysis
(i) Photoswitchable amidation
Fast
Slow
(ii) Photoswitchable polymerization

Fig. 2| Different types of switchable catalysis as temporal control. a| Switchable catalysis using different external stimuli. b| Redox-switchable catalysis. (i) Design of a redox-switchable metal catalyst. (ii) Redox-switchable polymerization using electrochemical setup. Fe(II) catalyst can polymerize lactide (red ball) while the Fe(III) catalyst can polymerize cyclohexene oxide (green ball). c| Chemoswitchable catalysis. (i) Anion coordination leads to allosteric change which unblocks the catalytic active center for the ring opening polymerization of ε-caprolactone. The red block denotes a bulky aromatic group that results in steric hindrance. (ii) Metal cation coordination onto the hemilabile crown ether moiety promotes the hydrogen activation reaction. (iii) Metal cation coordination to the oligomeric ethylene glycol chain increases ethylene polymerization activity. (iv) Presence of CO_2 prevents the polymerization of ε-caprolactone (blue ball) and initiates the ring opening copolymerization of CO_2 and cyclohexene oxide (green ball). d| Photoswitchable catalysis. (i) The catalyst can bind to the substrates via hydrogen bonds; in the E form the catalyst can bring the substrates closer and accelerate the amidation process, while the Z form separates the substrates apart and thus slows down the amidation. (ii) The diarylethene-type catalyst with a phenol moiety in the ring-opened phenol form incorporates more valerolactone (blue ball) while the ring-closed ketone form incorporates more trimethylene carbonate (purple ball) in the copolymerization process. (iii) By using different photocatalysts and changing the wavelength of light, the polymerization mechanism can switch between radical and cationic polymerization.

[H3] Redox-switchable catalysis

A challenge associated with achieving switchable catalysis is designing a system that has two (or more) different reactive states that can be accessed through application of external stimuli. Since redox reactions change the electronic configuration of a compound, which is intimately associated with its reactivity, an attractive option for switchable catalysts is through iterative addition of oxidants or reductants. A common way to carry out redox-switchable catalysis **[G]** is to design redox-active ancillary ligands[44-46] that are coordinated to a redox-inactive metal, which serves as the site for catalysis. This strategy was employed in the first example of redox-switchable catalysis,[47] when a rhodium complex supported by a cobaltocene bis(phosphine) was used for the hydrogenation and isomerization of alkenes. Despite this first example being applied to catalysis involving small molecules, the utility of redox-switchable catalysis has been exploited with more success in polymerization. For example, a titanium complex containing two redox-active ferrocene moieties appended to a salen (N,N'-bis(salicylidene)ethylenediamine) ancillary ligand (FIG. 2bi)[48] demonstrated redox modulation when used for the polymerization of lactide, with the reduced species being more active than the oxidized form of the catalyst. Since this report, several groups have utilized the ferrocene moiety for redox-switchable polymerization.[49-54] For example, using chelating ligands to position the ferrocene moiety in close proximity to the redox-inactive site for catalysis results in a greater difference in the reaction rate of the oxidized and reduced states of a catalyst (FIG. 2b). For example, while both forms of the above titanium complex demonstrated some activity for lactide polymerization, an yttrium complex showed complete on/off activity for lactide polymerization.[55]

An alternative method for redox-switchable catalysis is to use redox-active metals that serve as the redox-switching moiety and the site for catalysis (FIG 2bi). Catalysts based on several different redox-active metals have been explored using this strategy, with the most notable examples being ring-opening polymerization catalysts using cerium salfen[56] and iron bis(imino)pyridine complexes.[57] These catalysts

show similar behavior as that of polymerization catalysts utilizing redox-active ancillary ligands, demonstrating that it is not necessary to separate the redox-switching entity from the catalytically active entity.

A challenge associated with redox-switchable catalysis is the need to add oxidants and reductants to the reaction. When chemical redox reagents are used, purification of the product is required to remove the byproducts from the redox-switch. Moreover, adding chemical redox reagents to reactions that require gaseous reagents at elevated pressures requires specialized equipment. To address these limitations, an electrochemical potential can be used instead of chemical redox reagents for redox switching (FIG. 2bii). Such electrochemical potential can be achieved by employing bis(imino)pyridine iron complexes whose redox-active site is also the site for catalysis,[58] or catalysts that contain redox-switchable moieties installed in the ancillary ligand.[59]

While there are now many redox-switchable catalysts, a mechanistic understanding of how these systems perform redox switching is not well established. The oxidation state of the active catalyst and the efficiency of the redox switch are dependent on many factors. In addition to the proximity of the redox-switching moiety to the catalytically active site, another important factor is the identity of the metal center. For example, while the yttrium complex is active for lactide polymerization in its reduced state, the indium complex that contains the same ancillary ligand is active for lactide polymerization in its oxidized state.[55] The interaction between the metal center and the redox switchable moiety can be intricate; as revealed by computational and experimental studies,[60,61] the oxidation state of the redox active group can alter the Lewis acidity of the metal center, as well as change the energetic profile of the catalyst-substrate interaction.[62] Another factor is the identity of the reactant; some reactants may display orthogonal reactivity with respect to the oxidation state of the catalyst and some may not. For example, the iron complex shown in FIG. 2bii,[63] as well as other redox switchable catalysts,[51,53,55,60,64,65] is capable of polymerizing lactide selectively in its reduced form and epoxide in its oxidized form, but less selectivity is observed for lactones or cyclic carbonates.[61,64,66-68] The selectivity shown by each state of the system, i.e., orthogonal reactivity, is important in being able to combine multiple catalytic cycles without interference from the reaction that is turned off, for example. While more work is needed to understand these and other effects, two related factors appear to be important in polymerization catalysis: the propensity of the monomer to bind to the catalytically active site and the electrophilicity/nucleophilicity of reactive intermediates.[61,67,69] Both factors are altered by changing the oxidation state of the catalysts, and the relative importance of each is related to the nature of each reaction, including the identity of the metal centers and the monomers employed.

[H2] Chemoswitchable catalysis

Chemoswitchable catalysts are compounds that are responsive to the presence of external chemical additives. Unlike redox-switchable catalysis, chemoswitchable catalysis **[G]** does not involve alterations to the catalyst that leads to changes in their formal oxidation state. Because chemical reagents have a wide range of properties, they can trigger molecular events via various modes of action. For example, cations

can bind Lewis basic sites, whereas anions can bind Lewis acidic sites. Such interactions could turn a catalyst on or off, or modulate their reaction rates. Alternatively, chemical reagents could covalently modify a catalyst to produce another active species capable of achieving orthogonal reactivity.

The key design challenge in chemoswitchable catalysis is to enable a catalyst to change its structure and function by interacting with a chemical additive. One effective strategy for chemoswitchable reactivity involves regulating catalysis using anion coordination/dissociation to alter the metal complex geometry or block/unblock catalytically active sites. For instance, a supramolecular triple layer catalyst, comprising an aluminum salen complex flanked by two rhodium nodes equipped with biaryl blocking groups, was used for the chemoswitchable polymerization of lactones (FIG. 2ci). In the closed form, the rhodium centers are ligated by the amino donor of the supporting ligand, which positions the biaryl units above and below the aluminum active site.[70] Because aluminum is inaccessible due to the steric bulk of the amino arms, the catalyst cannot react with substrates. In the open form, chloride anions are bound to rhodium so that the amino groups are forced away from aluminum, opening up access to incoming monomers. When chloride salts are added, the triple layer catalyst reaches an open state that is active for the ring-opening polymerization of ε-caprolactone; when sodium salts are added, the chloride is abstracted from the rhodium centers, re-forming the closed catalyst state and almost completely stopping the polymerization. Remarkably, the molecular weight of the polymer increased linearly with conversion even as the catalyst was activated, deactivated, and reactivated, indicating an excellent control over catalysis.

Another strategy for chemoselective switching is to regulate catalysis using cations. By installing crown ether moieties in ancillary ligands, alkali metal cations can interact with the crown ether moiety to tune the electron density of the catalytically active site. This type of cation switching has been well-206 demonstrated in small molecule activation (FIG. 2cii).[71] For example, an iridium PCN-pincer complex was prepared containing an aza-crown ether macrocycle, which serves as a hemilabile ligand and cation receptor. When sodium or lithium tetraarylborate salts were added to a CD_2Cl_2/Et_2O solution of the compound, the free energy of aza-crown ether dissociation from iridium is lowered due to the favorable interaction of the alkali metal ion with the macrocycle. In the presence of these alkali metal cations, binding of dihydrogen becomes possible, and the cation-activated iridium species catalyzed H/D exchange with D_2 is significantly faster than the unactivated complex. This concept can be extended to a three-state (off/slow/fast) catalyst system, such as the positional olefin isomerization.[72] For example, iridium chloride complex is inactive for isomerization of allylbenzene; removal of the chloride produces a cationic species with hemilabile Ir–O interactions resulting in a slow catalyst. Addition of Li^+ salts to this cationic catalyst enhances the isomerization rate over 1,000-fold. The rate enhancement is attributed to cation–crown interactions making olefin binding more favorable, and increasing the amount of iridium that is actively engaged in catalysis. Another example of a cation-switchable system was used to achieve regioselectivity in positional isomerization: without salts added, alkenes were isomerized from the 1- to the 2-position; under the same conditions but with added Na^+ salts, 3-alkenes were observed instead.[73]

The cation coordination strategy of a catalyst can be used to tune not only the reaction rates but also the architecture of a polymer product.[74] For example, a family of nickel phenoxyimine complexes bearing

polyethylene glycol (PEG) chains can coordinate secondary metals (FIG. 2ciii); the addition of M^+ (where $M^+ = Li^+$, Na^+, or K^+) can produce 1:1 and 2:1 nickel: alkali species. The association constants between Ni and M^+ correlated with the size match between the ionic radius of M^+ and the chain length of the PEG chelator (larger cations require longer PEG chains and vice versa). Combining Na^+ or K^+ with the nickel catalysts featuring tri- or tetra-ethylene glycol chains increased the ethylene polymerization activity and gave polymers with higher molecular weight and branching density than the nickel catalysts alone. Cation-tuning was also applied to other olefin polymerization platforms and catalyst nuclearity was controlled through suitable ligand design.[75-78]

Small gas molecules can also be utilized as chemoselective switches by serving either as a trigger or a substrate for a reaction. For example, CO_2 can be used to oscillate a catalytic system between ring opening polymerization **[G]** (ROP) of a lactone and ring opening copolymerization (ROCOP) of epoxides and CO_2 (FIG. 2civ).[79,80] Another example of a small gas molecule switch is O_2. Although more well-known as a radical scavenger, O_2 can also be used in chemical transformations to generate radical species that can initiate radical polymerization.[81,82] Small gas molecules have the advantage of being easy to remove, however, a pressure reactor might be needed for the reaction.

Such examples demonstrate that chemical switching can be a useful strategy for regulating many different catalytic processes. Chemical switching can also take advantage of solution equilibria to tune reaction rates in a dynamic fashion. In cation tuning, different amounts or types of metal salts can be used to achieve different effects without requiring tedious synthetic modifications of the catalyst. Ideally, the chemical switch is only needed in catalytic amounts relative to the substrate (for example, in cation switching) or is incorporated into the reaction product (such as in CHO and CO_2 ROCOP). Some possible disadvantages of chemical switching are that the chemical reagents used are not traceless so they may need to be removed from the final product or they might not be compatible with subsequent steps in one-pot tandem or cascade reactions. Another potential limitation in cation switching is that the catalyst must be amenable to installation of secondary metal binding groups to achieve high cation responsiveness since Lewis acid additives are relatively commonly used to enhance activity.[83]

[H3] Photoswitchable catalysis

Photoresponsive processes are ubiquitous in nature and in artificial synthesis and catalysis. Photoswitchable catalysis involves a catalytically active species that can undergo a reversible photochemical transformation, which consequently changes its intrinsic catalytic properties.[84] In photoswitchable catalysis, photochromic functionalities such as azobenzenes, which can undergo an E-Z isomerization, and diarylethenes, which can undergo a photo-induced ring closing, are commonly employed.

The photoinduced E-Z isomerization of diarylethenes and stilbenes can lead to a change in the steric environment of the active site, which can block or unblock substrate access or bring substrates closer together or further apart, thus changing the catalytic activity.[85] Such azobenzene photochromic functionality has been used to control the rate of an amidation reaction (FIG. 2di).[86] For example, for the

amidation between aminoadenosine and adenosine-derived *p*-nitrophenol ester, a template molecule that contains two adenine receptors linked by an azobenzene spacer was designed. When the template molecule is in the E configuration, substrates bound to each receptor are far apart, resulting in a slow coupling rate. Upon UV irradiation (λ_{ex} = 366 nm), the template molecule undergoes a photo-induced isomerization, resulting in a photostationary state ratio of E:Z = 1:1. The *Z* configuration brings the two substrates in close proximity, thereby accelerating the reaction.

The photoinduced ring opening or ring closing of photochromic functionalities, such as spiropyrans[87,88] and diarylethenes,[89] results in steric and electronic changes that have been used to alter rates of lactone polymerization. For example, in a diarylethene-based system (FIG. 2dii),[90] the ring-opened phenol catalyst uses the exposed -OH group to activate lactide, which leads to a high polymerization rate. Upon UV irradiation (λ_{ex} = 300 nm), a photostationary state is reached, leading to 98% of the ring-closed ketone isomer, which shows a diminished polymerization rate. The system can be turned back on to the active state by irradiation with visible light. The different rates of the opened and closed forms toward valerolactone and trimethylenecarbonate (TMC) polymerization can also be harnessed to control the microstructure of the polymers. The ring-opened phenol catalyst, incorporates more valerolactone than TMC to synthesize copolymers with higher valerolactone content, while the ring-closed ketone isomer leads to a polymer with higher TMC than valerolactone content.

Unlike most redox-switchable and chemoswitchable catalysts, photoswitchable catalysis provides a non-invasive method to achieve temporal control since light is the only reagent required for switching. Consequently, product purification does not require removing excess reagents. Additionally, switching can be fast and not limited by mass transport.[91,39,92] A combination of different polymerization mechanisms can also be achieved by changing the wavelengths of light. For example, by using photocatalysts and a thiocarbonate chain transfer agent, cationic polymerization could be initiated by green light, while radical polymerization could be commenced by blue light (FIG. 2diii).[93] In terms of the experimental setup, light-emitting diodes are typically used as a source of light with specific and narrow wavelength. Although photoswitchable catalysis shows many advantages in temporal control, it also needs to overcome several hurdles such as obtaining a high photostationary state isomer ratio with a short irradiation time, finding isomers with orthogonal reactivity, and using UV light, which limits compatibility with some organic substrates or metal catalysts.

[H2] Spatial control

Spatial control in catalysis refers to the localization or separation of a catalyst from other species in reaction media. There are many reasons why spatial control is desirable, ranging from mitigating incompatibility between reagents/catalysts[8,13,18,20,21,23-27,94-99] to simple heterogenization of a catalyst to be recycled,[23,100-107] and opportunities to capitalize on local concentrations of reagents and effects that may occur from local magnetic or electric fields.[20,37,108-110] Spatial control may be realized in numerous ways, with the bulk of this work centered around confining catalysts within compartments,[8,13,20,23,25-27] using biphasic conditions,[111-114] and immobilizing catalysts onto supports.[100-103] The last few decades have

witnessed a steady growth in exploring the spatial control of molecular catalysts, with several reviews outlining the intricacies and caveats of localizing catalysts.[23,26,97,100] Here, the motivations and working principles for spatial control are discussed, all within the context of ultimately utilizing spatial localization to control multiple catalysts in proximity and circumvent potential challenges in integrating catalysis to carry out catalytic transformations that are not trivial for homogeneous catalysts.

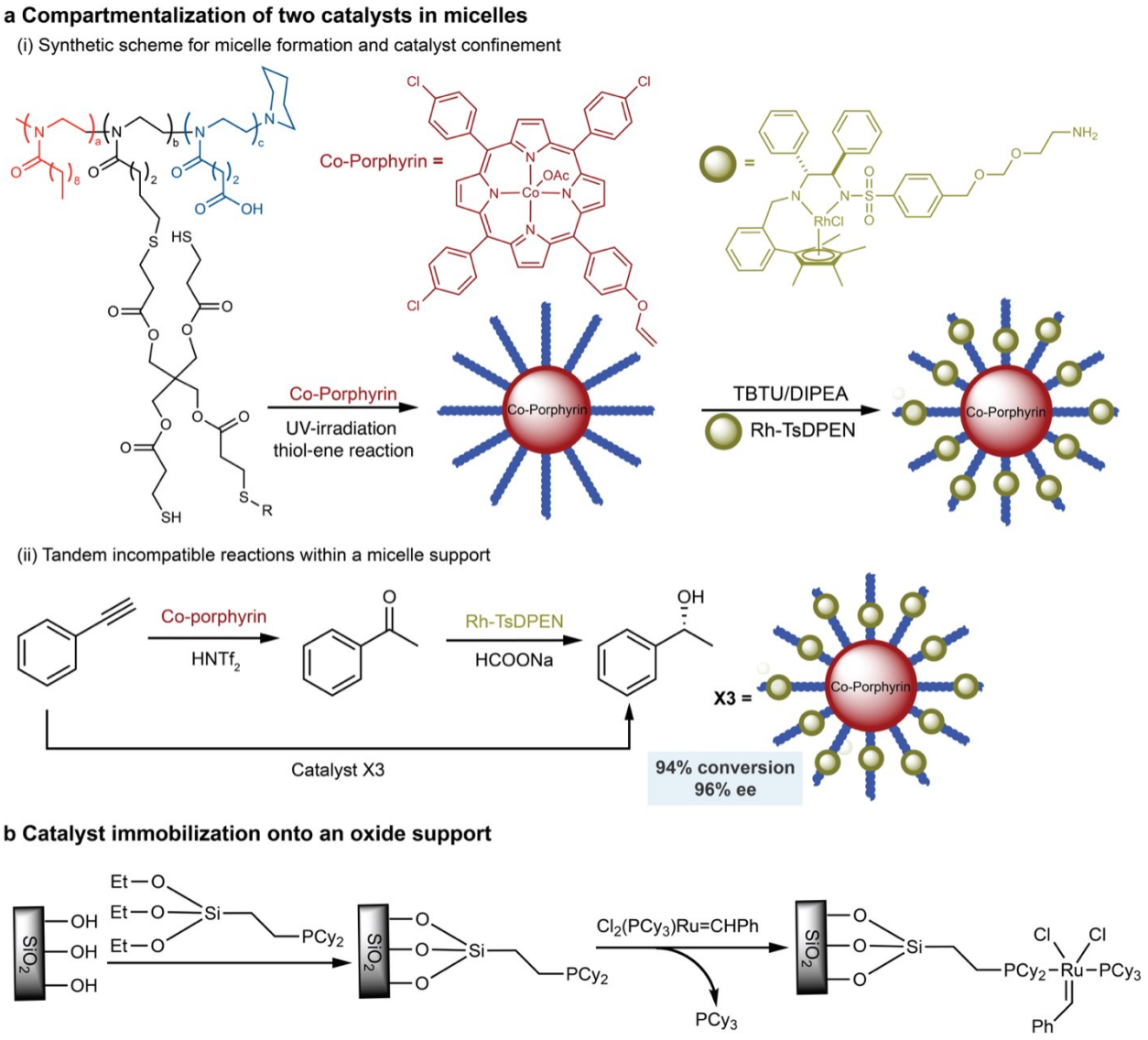


Fig. 3 | Approaches to spatial control via compartmentalization of catalysts in close proximity within confined spaces. a| (i) Micelle support with the synthetic scheme for micelle formation. An amphiphilic ABC-triblock copolymer was used to form the micelle support. The cobalt catalyst was covalently attached to the hydrophobic core (red and black blocks) via the thio-ene reaction, while the rhodium catalyst was attached to the hydrophilic arm (blue block). (ii) Tandem alkyne hydration and hydrogenation. b| Immobilization of two species in close proximity onto an oxide surface for synergistic catalysis.

[H3] Compartmentalization

Two major forms of spatial control are compartmentalization and surface immobilization **[G]**. The key challenge in compartmentalization is to design a system that keeps each catalyst inside a specific compartment while allowing reactants, intermediates, and products to move between the compartments. Compartmentalization has been reported in the biocatalytic literature as an approach for constructing efficient tandem catalysis by separating enzymes in well-defined micro- and nano-structures.[21,22,115-119] In doing so, compartmentalization results in beneficial circumvention of deactivating or competing pathways, retention of reactive or toxic intermediates, increases in reaction rates and high local substrate concentration.[21,22,115-119]. Inspired by the mechanistic work on in vivo compartmentalization, spatial organization at the nano- and microscopic levels has been implemented to construct in vitro biomimetic cascades with augmented catalytic performance.[22,26,95,99,117,120,121] For example, confining the β-galactose, glucose oxidase, and horseradish peroxidase in metal-organic frameworks led to an enhancement of the reaction yield in comparison to a freely diffusing enzyme.[26,95] Additionally, encapsulation of a nickel-iron hydrogenase in capsids enhanced the rate of H_2 production and improved the enzyme's thermal stability.[121]

Following the wealth of literature in applications of bio-compartmentalization, the organometallic community has subsequently made great strides in confining transition metal-based catalysts. Of relevance to integrated catalysis, compartmentalization may be used to construct efficient tandem, heterogeneous, organometallic systems that otherwise cannot be achieved with homogeneous catalysts.[8,13,18,20,27] The majority of prior confined organometallic catalysts focuses on employing macromolecular structures to tune selectivity in a manner unachievable in a homogeneous setting.[23] Additionally, the confinement of such catalysts often results in an improved stability and heightened activity over freely diffusing analogues.[23] Furthermore, compartmentalization has been applied to organometallic-mediated catalytic chain transfer polymerization, from which insight into the relationship between confinement and polymer modality has been extensively studied.[122-124]

Organometallic catalyst(s) can be compartmentalized by encapsulation in molecular cages to accelerate reaction rates and alter selectivity.[23,125-129] One example of compartmentalization is the selective recognition and stabilization of imminium ions by a Ga(III) catecholate molecular cage.[130] The compartmentalization of catalysts in molecular cages has been extensively applied in various reactions, such as aza-Prins cyclizations,[131] to promote kinetically disfavored pathways and thus steer selectivity.[131] One way to do this is using a micelle to support two co-encapsulated catalysts for incompatible catalytic reactions (FIG. 3a).[8] For example, in the direct conversion of an alkyne to an enantioenriched secondary alcohol, the Co-porphyrin catalyzed hydration of alkyne to ketone was not compatible with the Rh-TsDPEN catalyzed asymmetric hydrogenation of ketone to secondary alcohol, and when the two catalytic reactions were carried out in tandem, no product was detected. To bypass the issue, the cobalt catalyst was immobilized in the hydrophobic core of the micelle and the rhodium catalyst in the hydrophilic shell thus separating the two catalytic systems in two different domains to avoid interference. The intra-micellar diffusion of the ketone intermediate was fast enough to render high efficiency to the overall reaction.

Changing the local environment of a catalyst may understandably alter its catalytic properties, such as activity. Thus, in the realm of confinement via compartmentalization, a judicious design and choice of compartments will be paramount.[132] A likely pitfall of this approach may be a deleterious reduction in activity. To circumvent this, we point out a recent report that modeled the effect of varying compartment dimensions on catalytic activity for several common catalytic cycles.[27] Ultimately, a confinement must be employed carefully so that entry and exit into the compartment via diffusion is as fast as or slower than the kinetics of the catalytic cycle.

[H3] Surface immobilization

Another way to achieve spatial control over a reaction is by attaching a molecular catalyst onto a solid support material, also known as surface immobilization **[G]**.[28,30-35,133-135] A rich history of surface attachment of catalysts has led to a diverse lexicon: a compound can be attached, anchored, or immobilized to produce a surface-supported or surface-immobilized catalyst. Sometimes such systems are referred to as single-site heterogeneous catalysts because, ideally, the molecular nature of the catalyst leads to excellent homogeneity in catalyst activity and selectivity, while also boasting the benefits of a heterogeneous catalyst (for example, easy separation from reactants/products, facile recycling). An immobilized catalyst will only carry out the reaction where it is anchored to the surface, controlling the location of product generation. Furthermore, two or more catalysts can each be attached to a surface in order to prevent unwanted interactions and ensure catalyst compatibility, an invaluable aspect in integrated catalysis. For example, a palladium catalyst and an organic base were co-immobilized in close proximity onto a silica surface (FIG. 3b).[136-138] Synergism was realized by a significant acceleration (3 times higher conversion) of palladium catalyzed Tsuji−Trost allylic alkylation reactions with the co-immobilized palladium catalyst and organic base material, in comparison to a palladium catalyst on the silica surface without an organic base pair in close proximity.[136] In integrated catalysis, this approach may be adapted to co-immobilize two incompatibly catalysts, such as a metal/enzyme system,[139,140] to minimize transport between catalyst sites, while preventing deleterious interactions between them.

Considering the breadth of methods for surface attachment, ranging from covalent bonding to a silica surface or non-covalent interactions with modified surfaces,[28-35,133-135,141-143] the following should be considered when designing an anchored catalyst system. First, the application is important. Thermal reactions require a support that is robust under the reaction conditions, whereas electrochemical reactions require a conductive support and a linker that provides sufficient electronic coupling. Photochemical reactions generally require a transparent support, and often materials with a high surface area so that a sufficient amount of photocatalyst can absorb light. Second, the reaction mechanism is relevant. If multiple catalysts are required, the anchoring group should be sufficiently long and flexible to accommodate intermolecular interactions. If ligands dissociate, then the dissociating ligands should not be chosen for the attachment group to avoid catalyst leaching. Third, the reaction solvent is also important. Sequestration methods that rely on weak intermolecular forces, such as hydrophobic interactions, may be appropriate for reactions in water but not reactions that require nonpolar solvents. Finally, in terms of

the synthetic strategy to be used, sometimes it is more effective to anchor an organic group with a key functionality, and then use a different reaction to anchor the metal unit. For example, a silyl ether containing an azide can be attached to a surface, and then an alkyne-containing metal complex can be connected to the azide in a copper-catalyzed click reaction to form a robust linkage.[35]

[H2] Biocatalysis

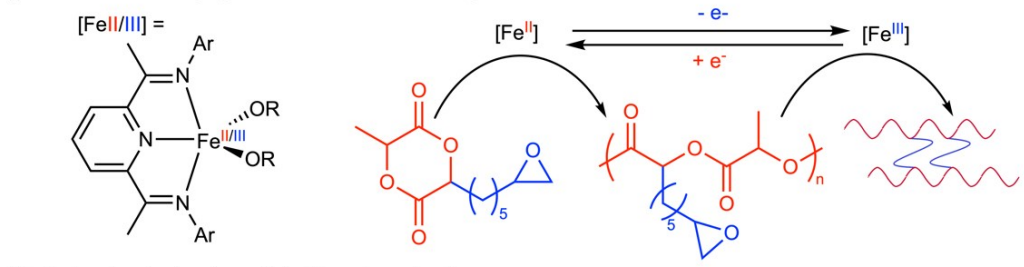
Biocatalysis has become a vital component in modern organic synthesis, spanning from academic research to industrial chemical and pharmaceutical processes.[144] Natural enzymatic catalysis is remarkable in its high activity and selectivity and mild working conditions. Although naturally evolved enzymes typically have a limited substrate scope, their performance may be enhanced by artificial enzyme engineering or integration with chemocatalysis for broader applications.[145] For instance, in dynamic kinetic resolution of amines and alcohols, an enantioselective enzyme catalyst was coupled with a racemization catalyst to maximize the reaction yield.[104] Furthermore, the spatial and temporal control methods developed for synthetic catalysis could also be applied to biocatalysis, providing new strategies to manipulate enzymes. For example, the integration of biocatalysis and photoredox catalysis has been developing rapidly in recent decades enabling otherwise challenging chemical transformations.[146,147] Spatial control approaches such as immobilizing enzymes onto heterogeneous supports[148] and crosslinking enzymes to form extended structures[149,150] can simplify the workup process and facilitate enzyme recycling.

Biology has many exquisite examples of systems that can manage complex reaction networks and perform efficient multistep reaction sequences.[21,24-26,95,96,116,117,119,120,151,152] Compartmentalization is a key spatial control feature that allows organelles to orchestrate how enzymes and substrates/intermediates interact, while simultaneously blocking entry of unwanted species. Discussed previously, compartmentalization is a major form of spatial control that biology also utilizes, wherein meticulously designed organelles localize enzymes and key substrates in close proximity to allow efficient channeling of intermediates between active sites, while simultaneously blocking entry of unwanted or exit of wanted intermediate species into or out of the confinement.[151,152]

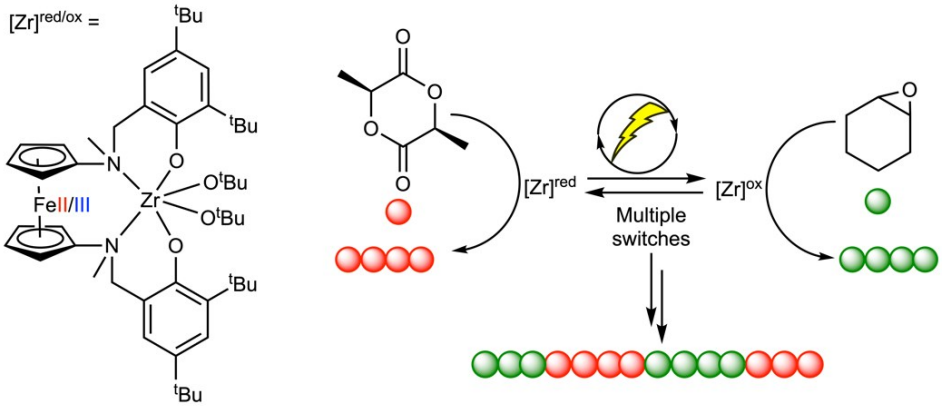
A representative example is the co-encapsulation of glucose oxidase and horse radish peroxidase within macromolecular scaffolds such as MOFs or polymersomes.[26,153] The cascade sequence between the two enzymes that consumes glucose shows drastically improved yields when the enzymes are confined versus the freely diffusing analogues. This method has been applied to many multi-enzyme systems, demonstrating that it is a robust strategy for creating complex yet efficient catalytic processes. Temporal control methods are also commonly used in biocatalysis, such as applying actuators or substrate gates to direct when each step of multienzymatic processes occurs.[154,155] The combination of enzymes with synthetic catalysts offers the best of both worlds, providing new opportunities to streamline chemical synthesis.[156]

a Switchable catalysis in polymer microstructure control

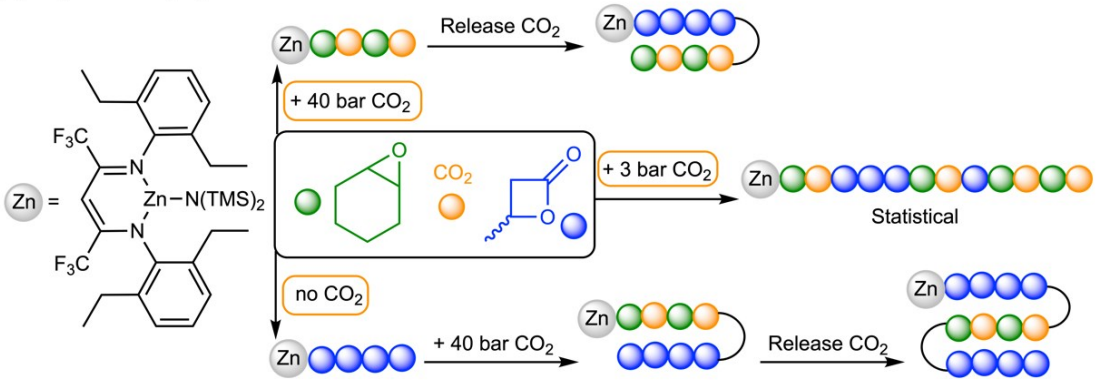
(i) Redox switchable polymerization and crosslinking



(ii) Electrochemical redox switchable polymerization



(iii) CO_2 controlled polymerization



b Polyethylene degradation by supported Ir catalyst

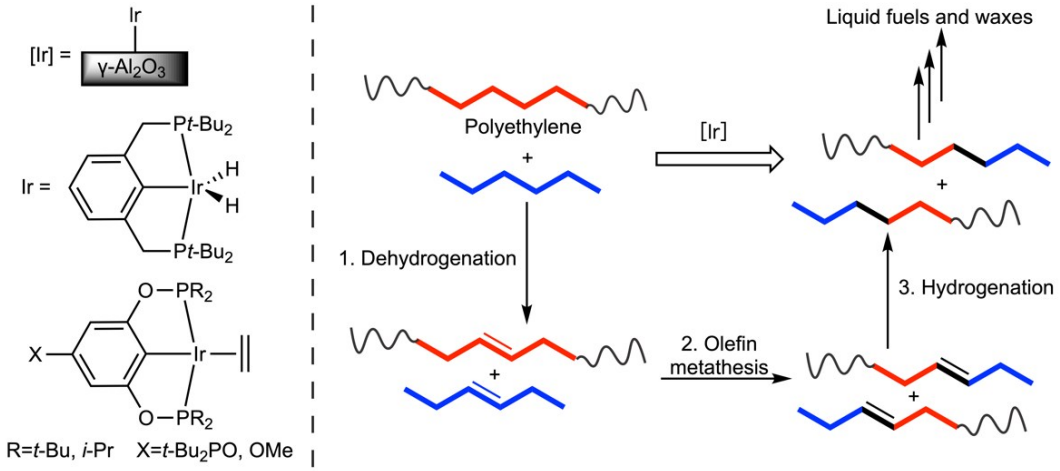


Fig. 4 | Temporal and spatial control in integrating different catalytic cycles. a| Harnessing activity of different catalytic states to control the polymer sequence and microstructure. (i) Redox-switchable catalysis toward the synthesis of a biodegradable crosslinked polymer network. (ii) Electrochemically controlled redox-switchable polymerization to synthesize a tetrablock copolymer. b| Polyethylene degradation via tandem (de)hydrogenation using γ-Al_2O_3 supported iridium complexes and alkane metathesis using Re_2O_7/Al_2O_3. The dehydrogenation/ hydrogenation process was catalyzed by the iridium compound while the olefin metathesis step was catalyzed by Re_2O_7/Al_2O_3.

[H2] Addressing catalytic compatibility

Spatial and temporal control approaches provide the means for coupling multiple catalytic cycles in a single reaction vessel. Spatiotemporal control may be utilized to couple different catalytic cycles by either exploiting the switchable catalysis of a single precatalyst or by reconciling incompatibility among multiple catalytic systems to generate products that would otherwise be difficult to synthesize. In this regard, polymerization reactions are the best examples to showcase how complex products can be generated from simple building blocks.

[H3] Cross-linking

Cross-linked polymer networks are valuable materials due to their high toughness and enhance thermal properties.[157,158] These materials are often synthesized using two-part resins or through the application of heat or light as a trigger for cross-linking. Each of these methods have different limitations such as the temperature required for heating and limited substrate penetration, respectively. The orthogonal activity of redox-switchable catalysis can be applied in the realm of polymer crosslinking to address some of these limitations (FIG. 4ai).[159] For example, when a bifunctional monomer that contained a cyclic diester and a pendant epoxide was polymerized upon exposure to an iron(II) complex, an epoxide-functionalized polyester was formed. By adding an external oxidizing agent, Fe(II) is oxidized to Fe(III), triggering the ring-opening polymerization of the epoxide moiety, thereby forming a crosslinked polymer network. Compared to linear poly(lactic acid), the cross-linked polymers show remarkably different thermal and physical properties. Moreover, the crosslinking method that capitalizes on the switching capability of the iron complex is beneficial because it does not require two-part resins, polymer creep is not an issue, and there are no limitations with respect to the thickness of substrates.

[H3] Switchable polymerization

Other sophisticated macromolecules can be synthesized by taking advantage of switchable polymerization reactions, such as block copolymers. Block copolymers demonstrate very useful properties by melding the properties of two different polymer classes. However, some block copolymers cannot be synthesized through sequential addition of monomers because the mechanisms for their polymerization may be very different. Consequently, these block copolymers are usually synthesized through sequential polymerization reactions that sometimes involve tedious and imperfect post-polymerization chain-end modifications to accommodate subsequent reactions. When encountering this scenario, switchable polymerization reactions are a good option to allow for the synthesis of block copolymers from pools of

monomers in a single reaction vessel. Electrochemistry has advanced redox-switchable catalysis by obviating the need for chemical oxidants and reductants, thus bypassing the incompatibility issue between substrates and redox reagents when the reaction is conducted in one pot. As such, electrochemically controlled redox-switchable catalysis have been employed to synthesize block copolymers in one pot.[58,59] For example, a ferrocene-containing zirconium compound is active in its reduced state for lactide polymerization, but inactive for epoxide polymerization (FIG. 4aii). When oxidized, the activity is reversed toward these two types of monomers. To achieve the synthesis of a multiblock copolymer, a one-pot setup was used with lactide and cyclohexene oxide monomers present at the beginning of the reaction to simplify the overall process, and electrochemistry was used to eliminate the need to add reagents during copolymerization. Using this strategy, a tetrablock copolymer was synthesized through sequential application of oxidative and reductive potentials. In addition to simplifying polymer purification, the electrochemical setup precludes possible side reactions, such as epoxide polymerization initiated by oxidants.

[H3] Solid supports

Spatially localizing a catalyst on the surface of a silica support is another important method that can be used to address compatibility issues. Although the general perception is that immobilizing the catalyst onto a surface reduces its activity due to hindered mass transport, the activity loss can be compensated with appropriate system modifications and optimization. For example, when various γ-Al_2O_3 supported iridium complexes (Ir@γ-Al_2O_3) used for alkane dehydrogenation and alkene hydrogenation were combined with a heterogeneous alkene metathesis catalyst (Re_2O_7/Al_2O_3), polyolefin degradation was observed when the polymer was combined with a light alkane (FIG. 4b).[160] By carrying out the alkane dehydrogenation in tandem with the olefin metathesis, alkanes are converted into substrates for alkene metathesis, the products from which are substrates for hydrogenation, thereby resulting in new alkanes. When the polymeric alkane polyethylene is combined with an excess of a light alkane, the result is smaller alkanes. Importantly, the dual nature of the iridium complexes used for alkane dehydrogenation and alkene hydrogenation enables the process, and requires that the supported iridium complex be used concurrently with the heterogeneous metathesis catalyst. Moreover, separating the molecular iridium complexes from the rhenium alkane metathesis catalyst circumvents any unwanted catalyst-catalyst interactions, which plagued similar reactions involving entirely homogeneous catalysts.[6] In addition, this system proved effective even when commercial polyethylene products, such as plastic bottles and food packaging were employed. This approach has also been employed in alkane upgrading by both homo- and heterogeneous Ir species,[161] the olefin degradation exampled discussed shows spatial control of multiple catalysts.

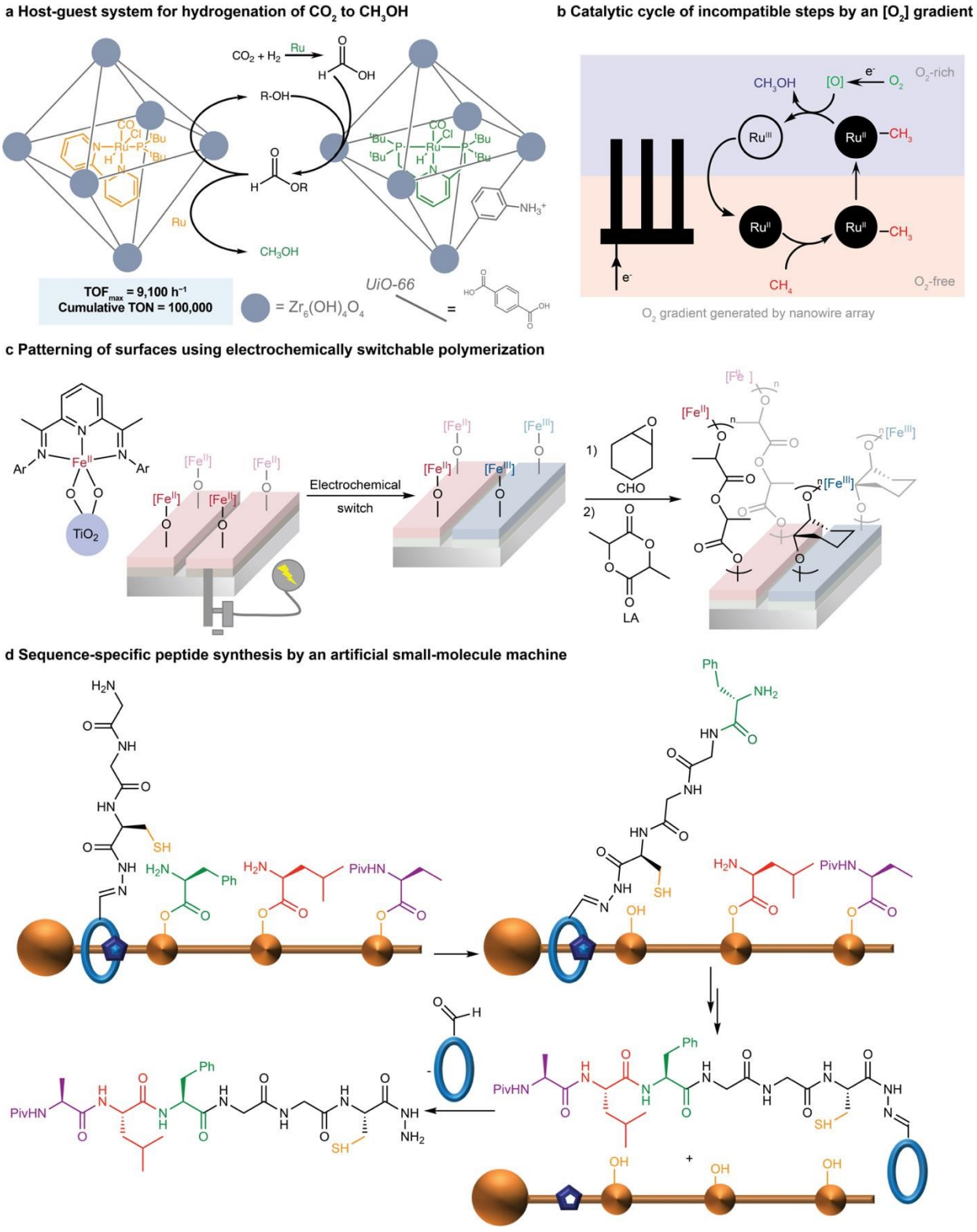


Fig. 5| Applications of integrated catalysis. a| Metal-organic framework (MOF) host-guest system for tandem CO_2 hydrogenation to CH_3OH via two separate ruthenium species encapsulated in a MOF (note: only one octahedral cage of the MOFs is shown for simplicity). b| O_2 mediated CH_4 oxidation to CH_3OH via an air sensitive Rh(II) intermediate

enabled in air by an electrochemically generated O_2 gradient. c| Integration of electrochemically catalyzed CO_2 reduction to CO and organometallic catalyzed ethylene/CO copolymerization for polyketone synthesis. d| Electrochemical control of a redox-switchable iron compound supported on a TiO_2 surface with two electronically isolated sections leading to different polymerization reactions. e| Sequence specific peptide synthesis by localizing the amino acid building blocks on a rotaxane.

[H1] Results

For temporal control, prior to reporting any catalytic results, it is essential to characterize the activity of the molecular catalyst in different states. NMR spectroscopy is the most commonly employed method for diamagnetic compounds, while other approaches like UV-vis spectroscopy can be used for paramagnetic compounds. When reporting the activity and selectivity of a catalyst in different states, vitality is important to rule out the possible interference coming from the external stimulus. Thus, control experiments should always be performed and reported. Furthermore, the addition and presence of a substrate in the reaction medium, i.e., from an incomplete reaction, may alter the nature of the catalytically active species and change its activity toward another substrate. Therefore, future research would benefit substantially from detailed experiment procedures, e.g., the concentrations and order of addition, when reactivity results are reported.

To confirm spatial control, one may employ a suite of characterization methods for heterogeneous systems. For example, in immobilizing a catalyst onto a surface, solid state NMR spectroscopy can help confirm and also determine the nature of a bound species.[162] Other methods such as FTIR spectroscopy can confirm the presence of key functional groups on the surface, while inductively coupled plasma - optical emission spectrometry (ICP-OES) can assess catalyst loading on the solid support.[33]

When combining two or more spatially controlled catalytic systems, mass transport between catalysts may understandably cloud reporting of reaction rates. In order to assess the extent to which mass transport alters observed reaction rates, the Φ criterion proves useful.[163,164] Developed in the middle to late 1900s, the Φ criterion can provide a qualitative assessment of mass transport. Derived from the reaction rate, concentration, diffusion coefficient of the species to be transported, and diffusion path length, if $\Phi < 1$, then one may ignore diffusional effects on reported reaction rates and kinetics. However, if $\Phi > 1$, one cannot ignore the effect of mass transport. In addition to providing insight into the interplay of mass transport and kinetics in integrated catalysis, the Φ criterion can also provide a justification for exploring ways to alleviate mass transport (vide infra).

[H1] Applications

Integrated spatiotemporally controlled catalysis, although rare, has been employed to construct sophisticated systems and solve compatibility problems between multiple catalytic cycles. Such applications include small molecule activation, polymerization, and surface patterning. Although the development of integrated catalysis is still in its infancy, and some examples are not strictly, by definition,

an integrated system, they demonstrate the potential of integrated catalysis and how it can be exploited in synthesizing products with high complexity.

[H2] Confinement

Integrated catalysis can address thermodynamic constraints in sequences of chemical reactions. For example, the power of encapsulating transition metal catalysts in metal organic frameworks (MOFs) for integrated catalysis was recently demonstrated for the efficient hydrogenation of CO_2 to methanol.[19,165] In this example (FIG. 5a), two different ruthenium complexes were encapsulated in UiO-66, enabling a tandem catalytic reaction in three steps: the thermodynamically unfavorable hydrogenation of CO_2 to formic acid catalyzed by a PNP ruthenium complex; the near thermoneutral conversion of formic acid to formate ester catalyzed by the zirconium oxide nodes of UiO-66; the thermodynamically favored hydrogenation of formate ester to methanol catalyzed by a PNN ruthenium complex. This catalyst system overcomes the thermodynamic limitations associated with the hydrogenation of CO_2 to formic acid by coupling it with the thermodynamically favored hydrogenation of formate esters. If the first step was separated from the second two in a sequential process, no formic acid would be obtained. Importantly, no methanol was observed unless at least one of the two ruthenium-based complexes was encapsulated in UiO-66, and catalyst recyclability was only possible if both ruthenium complexes were encapsulated in UiO-66. These observations highlight the benefits of catalyst compartmentalization to prevent undesired catalyst-catalyst interactions.

[H2] Concentration gradients

Another form of spatial control that has been beneficial for integrated catalysis is the generation of local concentration gradients, which can be conveniently achieved electrochemically. Depending on the steepness of the gradient, areas rich or void of certain species may be loosely defined as compartments. For example, a nanowire-array electrode can be employed to reconcile incompatibility between CH_4 activation by an O_2-sensitive rhodium(II) metalloradical with O_2-based oxidation for CH_3OH formation (FIG. 5b).[20,166] A reducing potential applied to the nanowire array electrode generated an O_2 gradient along the wire, and an anoxic, essentially O_2 free zone was established at the bottom of the wires. As a result, an efficient catalytic cycle was established in which the air-sensitive Rh(II) activated CH_4 in the anoxic region, whereas CH_3OH synthesis proceeded in the aerobic region with O_2 as the terminal oxidant. When a planar electrode was used, such a result was unattainable, showing that the O_2 gradient of the nanowire array was responsible for reconciling incompatibility. The effective detainment of the ephemeral Rh(II) intermediate by the nanowire electrode for catalytic CH_4-to-CH_3OH conversion[20,166] encourages further exploration in utilizing microscopic concentration gradients in catalysis to reconcile incompatibility.

A similar strategy using the electrochemical method to control the concentration of small molecules can also be applied in generating CO from CO_2 then utilizing the produced CO as a building block in subsequent reactions. Considering that CO_2 is abundant and is one of the culprits of climate change, deriving reactive building blocks from it and converting them into value-added products would be ideal and could benefit substantially from integrated catalysis. For example, CO produced from CO_2 was utilized as the carbon feedstock in reactions such as Fischer–Tropsch, hydroformylation, and carbonylation.[167] Furthermore, in

reactions like CO and ethylene copolymerization, the pressure of CO was fine-tuned electrochemically, and the amount of CO incorporated was modulated in an integrated catalytic system to control the structure of the resulting polyketone (FIG. 5c).[168]

[H2] Solid-state polymerization

Integrated catalysis can generate highly complex products, such as a precisely controlled macromolecular structure,[58,59,169,170] but the spatiotemporal control that is inherent to integrated catalysis has also been exploited to synthesize patterned polymer-functionalized surfaces (FIG. 5d).[171] By immobilizing redox-switchable bis(imino)pyridine iron polymerization catalyst to semiconducting TiO_2 nanoparticles, redox-switchable polymerization reactions can be carried out in the solid state. Suspending the iron(II)-functionalized TiO_2 nanoparticles on conducting fluorine-doped tin oxide surfaces led to electroactive surfaces whose chemoselectivity for polymerization can be altered through the application of an electrical current: surfaces with the catalyst in the iron(II) oxidation state react with lactide to form polyesters while surfaces that have been exposed to oxidizing potentials result in oxidation of the catalyst to the iron(III) oxidation state, which reacts with epoxides to form polyethers. By using fluorine-doped tin oxide substrates that contain electrically isolated zones of the functionalized TiO_2 nanoparticles, patterned surfaces containing polyesters and polyethers can be synthesized by applying oxidizing potentials to zones where polyethers are desired.

[H2] Molecular machines

Another example of synthesizing products of high complexity is the application of a molecular machine in peptide synthesis. An artificial molecular machine was developed to mimic nature's ribosome and synthesize oligopeptides with a predetermined sequence (FIG. 5e).[170] The system consists of a rotaxane, an axle with protected amino acids immobilized to it, and a bulky end-stopper. The rotaxane has a polypeptide arm that contains a cysteine moiety and a terminal glycylglycine amine group. The oligopeptide synthesis is accomplished by a series of O-S and S-N acyl transfers as the rotaxane moves along the axle. Though the system is only capable of incorporating up to 4 amino acids and is not catalytic, it still represents a valuable proof of concept that demonstrates how artificial synthesis can mimic nature. Furthermore, it illuminates an encouraging direction that, beyond stoichiometric templating, an integrated system, showing spatial and temporal control, may be able to deliver the synthesis of highly complex products.

[H2] Automation

Finally, the benefits of integrated catalysis are amenable to future automation strategies, such as the Chemputer. Like in biocatalysis, where high-throughput screening can help identify the best protein from the vast genome database among numerous candidates and myriad mutations, integrated catalysis could also benefit from a highly automated synthesis-characterization-analysis system when devising a complex system involving multiple catalytic cycles to optimize the working conditions, e.g., solvent, temperature, concentrations, and cocatalyst. Other than the well-established peptide and nucleotide syntheses, laboratory-scale synthesis of complicated products is still mainly performed manually. The Chemputer demonstrates an efficient automation of multistep synthesis and purification processes (FIG. 6).[172] By

using programming, various synthetic procedures can be abstracted from written protocols, translated into machine language and implemented on synthetic modules to prepare pharmaceutical compounds. The Chemputer may be as or more efficient than a traditional iterative lab approach, without any human intervention. Furthermore, the Chemputer was specifically designed to be amenable to variations in the sequence of steps performed, to allow adaptation to a wide array of chemical processes. In addition, such a synthetic platform allows for the standardization of chemical synthesis, minimizing irreproducibility caused by the synthetic nuances that are often omitted or assumed already known by the reader.[172,173]

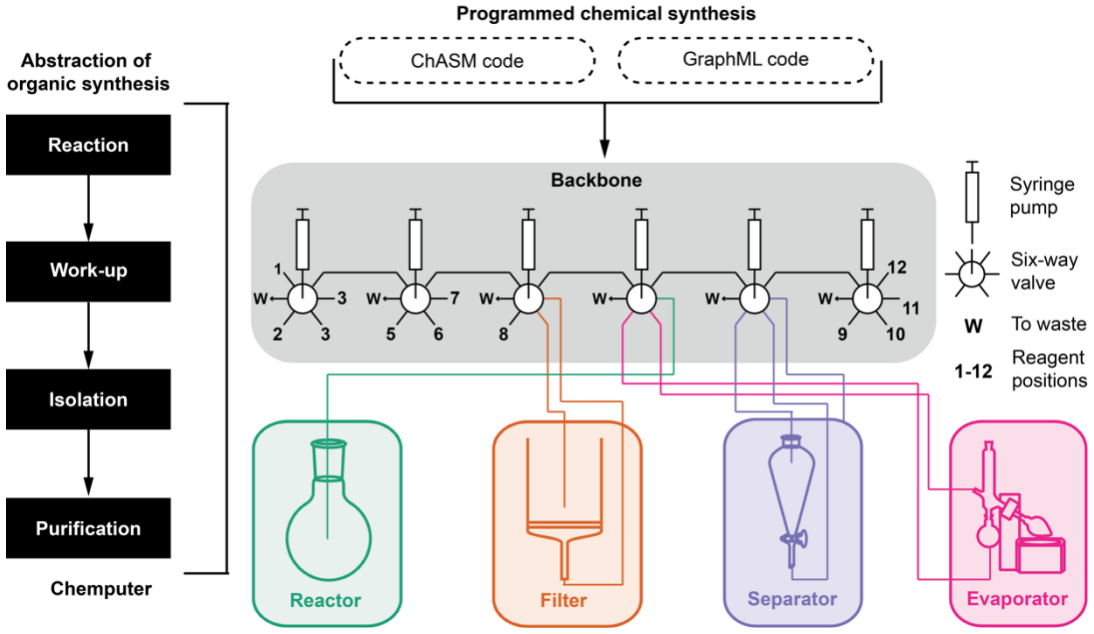


Fig. 6| **Organic synthesis in a robotic system** enabled by the application of a chemical programming language to an automated synthetic set up.

[H1] Reproducibility and data deposition

[H2] Reproducibility

The degradation of catalysts during a reaction is one of the main problems in catalysis. Degradation has an even more profound impact on switchable catalysis, as the switching process introduces additional possible degradation pathways. Therefore, a judicious choice of the most compatible external stimulus may be the key to successful switchable catalysis. In addition, for catalysts confined onto surfaces, mass transfer may slow down the overall reaction rate and is influenced by the distance and diffusivity between the two catalysts. While this property can be exploited for integrated catalysis (for example, capitalizing on local concentration gradients), if the physical location or diffusivity of the catalysts is not well controlled (stirring, solvent, temperature), irreproducible results can be problematic.

In addition to the chemical and engineering complications that exist with integrated catalysis, there also is an analytical challenge to address when catalysts are spatially confined. For homogeneous catalytic systems, the characterization methods are diverse and often diagnostic, such as NMR spectroscopy and

X-ray crystallography. However, when the catalyst is compartmentalized or immobilized on a solid surface, the system becomes complex, and characterization needs to involve relatively complicated techniques. Some spectroscopic methods such as X-ray photoelectron spectroscopy, inductively coupled plasma mass spectrometry (ICP-MS), and ICP-OES can be used to obtain elemental information either for the surface or the bulk powder. Infrared, Raman, absorption, and solid state NMR spectroscopy can facilitate understanding the nature of the active species. However, additional characterization methods are necessary for a detailed and precise chemical structure of the catalytic system that would ensure reproducibility. Especially in an integrated system, using operando techniques to understand the mechanism of the reaction and the interactions between catalyst-catalyst, catalyst-substrate, and substrate-substrate under working conditions will be extremely beneficial.[174,175]

[H2] Database

The field would benefit from a database of coupled tandem to use as a reference when constructing complicated integrated catalytic systems. When possible, the catalytic reactions involved, the spatiotemporal control methods and reaction conditions employed, and how the activity and selectivity of the overall reaction compared to the isolated stepwise reactions should be deposited. A database of the resulting products would also be informative. In the case of polymerization reactions, for example, many copolymers are synthesized using tandem polymerization reactions, and while there are databases listing the structures and properties of polymers, such as PolyInfo, Polymer Property Predictor and Database, and CAMPUS, these databases are far from comprehensive in summarizing the structures and corresponding properties of the various copolymers produced and reported. If this information could be benchmarked and centralized, it could provide guidance for future polymer design and retrosynthesis.

[H1] Limitations and optimizations

A major limitation of the current state of iterative chemical synthesis is inefficiencies related to time and material involved in workup steps, which may also lead to decreased yields.[176] An integrated catalytic approach can alleviate this drawback, as well as pave the way to obtaining complex products from simple feedstocks. As a field that continues to evolve, integrated catalysis still faces many challenges. First is the issue of compatibility. Compatibility considerations in integrated systems is multifaceted and includes the compatibility between catalysts, reagents, solvents and reaction conditions. When different reaction cycles are carried out in one pot, the catalysts may undergo deactivation or decomposition caused by the substrates or cocatalysts of another reaction. In principle, switchable catalysis circumvents the problem by generating different catalytic species at different times, while spatial control can be used to separate different precatalysts. Furthermore, when different reactions require different conditions, such as temperature and pressure, reconciling such disparity is pivotal. Again, spatial control becomes important by separating such reactions in different microenvironments (such as compartmentalization, immobilization, or electrochemically generated concentration gradients).

Limitations and potential drawbacks may be related to the temporal control of a catalyst. For example, the mode of temporal control (photochemical, electrochemical, or chemical) may not be compatible with other reagents in the reaction medium. An applied potential or light source that switches a catalyst

between active states may have undesired consequences on other species in solution. One method to circumvent this incompatibility would be to spatially separate the species of interest. For example, if a catalyst is to be switched electrochemically, immobilizing it onto the electrode surface may help prevent some unwanted redox reactions with other species. However, if the other species are free to diffuse, they may still be decomposed by an applied potential. Further, compartmentalization of the incompatible species could also help. Thus, great care must be taken to ensure other species in an integrated system are compatible with the means of temporal control.

With respect to spatially localizing a catalyst, mass transport can become important. The heterogenization of a previously homogeneous catalyst introduces transport from the bulk solution to the catalyst site as a fundamental step for catalysis to proceed. Should this step prove limiting, it may be counterproductive to spatially control a catalyst. Instead of relying solely on diffusion, the introduction of fluid transport may help overcome mass transport limitations.[177-181] Further, conducting a reaction in flow provides numerous additional parameters, such as flow rate and residence time, providing more opportunities for optimization compared to a batch process. Mass transport limitations may also be exploited to avoid unwanted background reactions. This would greatly depend on the pervasiveness of such mass transport limitations, as well as the competition between diffusive and kinetic phenomena.[164]

When employing spatiotemporal control to build an integrated catalytic system, one must take into account some key considerations. The compatibility and practicality of all components of an integrated system should be considered. First, all possible combinations of controls should be tested to assess compatibility between catalysts, catalysts and reactants, and reactants. Simple outputs such as percent conversion can be used to assess the effect of one reagent on another with respect to maintaining or diminishing activity. In addition, assuming the separate catalyst systems have different optimal conditions (such as temperature, solvent, pressure) compatible middle ground conditions must be determined. In the event there is an incompatibility between some reagents in the two systems, spatial and/or temporal control may be implemented to circumvent the mutual deactivation.

For spatial control, a key consideration is whether the catalyst/reagents need to be separated or can feasibly be immobilized onto a surface or confined within an easily accessible compartment. For temporal control, when incorporating switchable catalysis to either achieve on/off control or to open more avenues for different reactions, electronic effect of a redox catalyst, the ring opening/closing of a photochromic moiety, or the metal cation coordination onto a pendant ligand can be used, depending on the reaction conditions. For example, if the reagents/substrates/products in the system are colored, then it might be easier to add a redox-switchable or metal cation coordinating moiety to the ligand framework to realize a switch in catalytic activity rather than employing light as the external stimulus. On the other hand, if switchable catalysis requires intercepting short-lived reactive intermediates, then light may be the most appropriate external stimulus to target. The next thing to consider is whether the exogenous trigger interferes with the catalytic transformation itself. If the system is non-colored and remote control is preferred, then a photoswitch or an electrochemical switch are the most viable options as neither technique requires adding reagents to the reaction. Finally, practicality is as equal if not the most important consideration. The most intricate spatial and temporal methods may be developed and applied

to address any conceivable compatibility issues. However, the time and effort spent should not be greater than that of the combined systems treated independently. Thus, researchers must critically evaluate and determine what compatibility issues need to be addressed before considering what spatial and/or temporal methods to use and whether an integrated approach is superior to an approach involving sequential catalytic reactions.

[H1] Outlook

In integrated catalysis, different reactions are coupled in a single vessel to generate products with high complexity from a mixture of abundant starting materials. Inspired by macromolecule synthesis in living cells, artificial catalysis for the synthesis of polymers with a well-defined sequence and microstructure has been achieved in one pot with the proper utilization of integrated spatial and temporal control. Biological macromolecules, such as proteins and DNA, encode information in their sequences and structures. Likewise, the sequence and structure of synthetic macromolecules dictate their properties. We envisage that integrated catalysis can become the machinery for synthesizing novel molecules and materials with distinct properties. In addition to macromolecules, integrated catalysis can also be an effective tool for multistep syntheses, and asymmetric syntheses of organic small molecules, such as pharmaceuticals.

Careful design of catalyst combinations in tandem catalytic cycles may enable reactions to proceed under mild conditions and improve the selectivity and yield of the overall process. More importantly, integrated catalysis can capture unstable, transient, and hazardous intermediates,[182-184] and subsequently convert them into stable and valuable products, thus expanding synthetic capabilities. For example, by coupling an exothermic and endothermic reaction, thermodynamic leveraging in tandem reactions can drive the formation of otherwise unviable products.[19,165,185,186] Furthermore, breaking down a thermodynamically favorable but high activation energy reaction into a series of steps that can be optimized individually, can lower the overall energy barrier and allow the reaction to proceed through milder conditions.

To achieve precisely controlled and widely applicable integrated catalytic systems, it is imperative to enrich and update the toolbox available by adding emerging methods for spatial and temporal control. As a complement to artificial catalysis, biocatalysis is also indispensable, and often provides exquisite selectivity. Thus, the construction of hybrid catalyst systems that involve biocatalysis and artificial spatial-temporally controlled catalysis is an exciting new direction for integrated catalysis.[145] Finally, when implementing integrated catalysis, engineering aspects such as reactor design are also crucial to ensure that the anticipated results can be achieved.

Another way to facilitate the design of integrated catalytic systems is to use simulations and predictions that evaluate structure-activity-selectivity relationships to identify the best catalyst in a timely manner. Recent advances in quantum mechanical and finite element simulations now make possible an holistic analysis of the entire integrated system that takes into account all contributing factors.[187] In this regard, screening of catalysts for isolated reactions should be coupled with first-principles calculations and data science to optimize the integrated system. Computer-assisted calculations can also be used in conjunction with high-throughput automation[188] to further expedite screening and streamline the synthetic routes to achieve high efficiency, low waste, and low cost.

Glossary

Cascade / Domino process: A transformation that installs two or more bonds under identical conditions and with the same mechanism.

Chemoswitchable catalysis: A reaction in which the selectivity of a catalyst can be reversibly altered by a chemical trigger.

Compartmentalization: Spatial localization of one or multiple species within a well-defined encapsulation or confinement, where entry and exit within the compartment is dependent on the chemical makeup of both the compartment and diffusing species.

Orthogonal reactivity: Reactivity of a multistate catalyst toward different substrates: catalyst is active in one state for one type of reaction and inactive for another, and shows the opposite trend in the other state.

Redox-switchable catalysis: The reactivity or selectivity of a catalyst that can be reversibly altered by changing its oxidation state.

Ring opening polymerization: A chain growth polymerization reaction in which the polymer chain propagation is achieved by the reactive terminus attacking and ring opening a cyclic monomer to elongate the polymer chain and generate a new active terminus.

Surface immobilization: Spatial localization of a typically homogeneous species onto a heterogeneous support.

Tandem process: Coupled catalytic processes in which substrates are converted sequentially by two or more mechanistically distinct reactions.

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Competing interests

The authors declare no competing interests.

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Summary: This paper presents how spatially separating an alkane dehydrogenation/hydrogenation catalyst and an alkene metathesis catalyst can circumvent unwanted catalyst-catalyst interactions.

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Summary: This paper details the immobilization of Fe(II) and Fe(III) bis−iminopyridine catalysts onto an electrochemically active surface to generate patterned polylactide and poly(cyclohexene oxide) surfaces via switchable ring opening polymerization.

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