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Kinetically controlled phenomena in dynamic combinatorial libraries

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Dynamic combinatorial libraries (DCLs) are collections of structurally related compounds that can interconvert through reversible chemical reaction(s). Such reversibility endows DCLs with adaptability to external stimuli, as rapid interconversion allows quick expression of those DCL components which best respond to the disturbing stimulus. This Tutorial Review focuses on the kinetically controlled phenomena that occur within DCLs. Specifically, it will describe dynamic chiral resolution of DCLs, their self-sorting under the influence of irreversible chemical and physical stimuli, and the autocatalytic behaviours within DCLs which can result in self-replicating systems. A brief discussion of precipitation-induced phenomena will follow and the review will conclude with the presentation of covalent organic frameworks (COFs)—porous materials whose synthesis critically depends on the fine tuning of the crystal growth and error correction rates within large DCLs.

Key learning points

(1) Dynamic combinatorial libraries (DCLs) are collections of compounds that can interconvert through reversible chemical reaction(s). Because of this reversible behaviour, DCLs can respond to external stimuli by amplifying their components that best adapt to those stimuli.

(2) DCLs also engage in behaviours that are irreversible and proceed under kinetic control. These include dynamic resolution, self-sorting and self-replication, irreversible "fixation," as well as irreversible and selective dynamic resolution through fractional precipitation.

(3) Dynamic resolution, self-sorting and self-replication all represent kinetically controlled behaviours in which different components of a DCL react at different rates. In self-sorting, dynamic resolution is iteratively repeated until no starting materials remain, while self-replicating molecules catalyse their own production from the DCL, leading to their non-linear amplification at the expense of DCL members without autocatalytic properties.

(4) Precipitation of individual DCL members essentially irreversibly removes them from the library, as the exchange reaction between the solution and the precipitate slows dramatically. Fractional precipitation of DCLs has been used in the context of dynamic diastereomer resolution, self-sorting and synthesis of interlocked molecules such as Solomon knots and Borromean rings.

(5) Covalent organic frameworks (COFs) are insoluble extended structures constructed through a reversible reaction of oligofunctional precursor(s). These materials have applications in gas storage and separation, as conductive and semiconductive materials, and as light-harvesting platforms.

Introduction

A chemist has only two problems: thermodynamics and kinetics.† This jovial statement strikes at the heart of the issue of product control in synthetic chemistry: while these two sets of parameters control all of the reaction's intricacies, they are fully understood only for a small number of the currently used synthetic transformations. In reactions proceeding under *thermodynamic control*, product distribution is directly related to the relative stabilities of products. On the other hand, *kinetically controlled* reactions generate products in ratios that are correlated to the relative rates of corresponding products' formation, and thus in turn to the relative activation energies. To a certain extent, kinetic and thermodynamic control can be imposed onto the system through variations in the reaction conditions. High temperatures and equilibration catalysts tend to favour thermodynamic products, since they facilitate system's travel across the energy landscape. Conversely, low temperatures and highly reactive reagents disfavour reverse reactions and ensure dominant kinetic control. Often, the most stable products also form the fastest, meaning that the kinetic and the thermodynamic product is one and the same.[1,2]

Dominant kinetic and thermodynamic control represent the two extremes of reactivity, and numerous reactions reside along the continuum between the two. In such cases of mixed

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† The corresponding author is convinced that this sentence was—in some similar form—uttered by a famous chemist. However, numerous inquiries with some of the leaders in the field of physical organic and supramolecular chemistry failed to reveal the author of the quote.

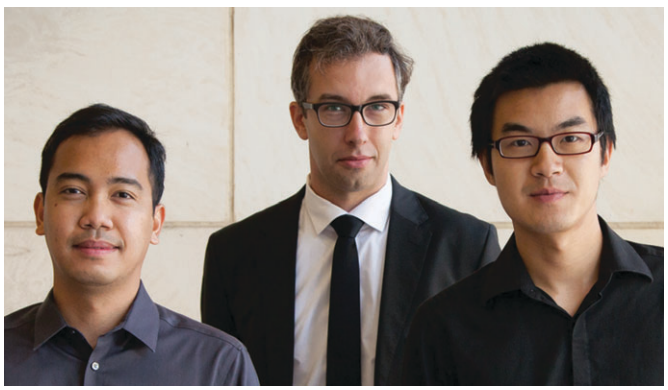
thermodynamic and kinetic control, prediction of product distribution is less intuitive, but at the same time potentially tuneable by the above mentioned drivers of kinetic and thermodynamic control. If the reactive system's kinetic and thermodynamic parameters are sufficiently well understood, two-dimensional control of reactivity could potentially be achieved. However, synthetic organic chemistry traditionally shunned away from equilibrating mixtures, and has predominantly focused on the use of kinetically controlled reactions. In recent years, the thermodynamically controlled *dynamic combinatorial chemistry* (*DCC*)[3–7] emerged as an appealing complement to the kinetically controlled reactivity. In DCC, the reaction's reversibility constitutes a convenient error-correction mechanism, and DCC can produce the thermodynamically most stable species in virtually quantitative yields. While scarcity of suitable reversible reactions still limits DCC's applicability, Zhang's recent review tallied 35 well-behaved reversible reactions that have been used in the context of DCC.[8]

This review will focus on the kinetically controlled phenomena that occur within *dynamic combinatorial libraries* (*DCLs*). The potential benefits of combining DCC with kinetically controlled reactivity are: (a) the use of irreversible reactions allows the generation of stable, isolable products, and (b) permits isolation of DCL components (or their derivatives) that are not thermodynamically most stable. Furthermore, (c) systems under combined kinetic and thermodynamic control may represent better models for living systems—which use many reversible interactions, but rarely operate at equilibrium. This review will first summarize the energy profiles for several cases of mixed thermodynamic/kinetic control. Then we will move onto the examples of phenomena that utilize this combination of kinetics and thermodynamics to achieve (a) DCL trapping, (b) dynamic chiral resolution, (c) self-sorting and (d) self-replication. Finally, we will highlight some recent examples of (e) precipitation-induced phenomena and (f) the use of DCLs to produce covalent organic frameworks (COFs).[9] The aim of this Tutorial Review is not to be comprehensive, but rather to illustrate the diverse trends in applying kinetic parameters to dynamic combinatorial libraries. Therefore, some excellent examples will by necessity be omitted, and we apologize in advance to authors whose work will be neglected.

Energetics of dynamic combinatorial libraries (DCLs)

The field of dynamic combinatorial chemistry has been extensively reviewed in recent years.[3–7] Kinetically controlled processes in DCLs have not been an explicit focus of a review, but we refer the readers to Philp's perspective on the use of recognition-mediated amplification of DCL components in the context of dynamic resolution and self-replication.[10]

By their very definition, DCLs are collections of rapidly equilibrating molecules, meaning that their energy profiles are quite shallow and that all local maxima are accessible to an average molecule. Such a situation is illustrated in Fig. 1A, where the two possible states of a simple DCL can communicate with each other *via* a low activation barrier that corresponds to the readily reversible reaction. At the same time, all other reactions are restricted to the DCL components, and thus no material leaves the DCL through a side reaction. This situation represents "classical" DCC which does not include irreversible reaction processes. It has been extensively reviewed,[3–7] and will not be discussed here. In contrast, the situation presented in Fig. 1B illustrates a non-dynamic library of molecules, where multiple states do exist, but cannot communicate as they cannot traverse the high internal barrier. This situation means that there is no DCL and will also not be further discussed.



Rio Carlo Lirag, Ognjen Š. Miljanić and Qing Ji

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Ognjen Š. Miljanić (center) was born in Belgrade, then Yugoslavia, in 1978. He holds a Diploma (2000) from the University of Belgrade and a PhD (2005) from the University of California at Berkeley, the later earned in the group of Prof. Peter Vollhardt. Following a 2005–2008 postdoctoral stay at UCLA with Sir Fraser Stoddart, Ognjen joined the University of Houston (UH) as an Assistant Professor. His research interests include dynamic combinatorial libraries, metal–organic frameworks and organic fluorophores. He is the recipient of the 2012 NSF CAREER and UH Teaching Excellence awards, and a 2013 Cottrell Scholar of the Research Corporation for Science Advancement.

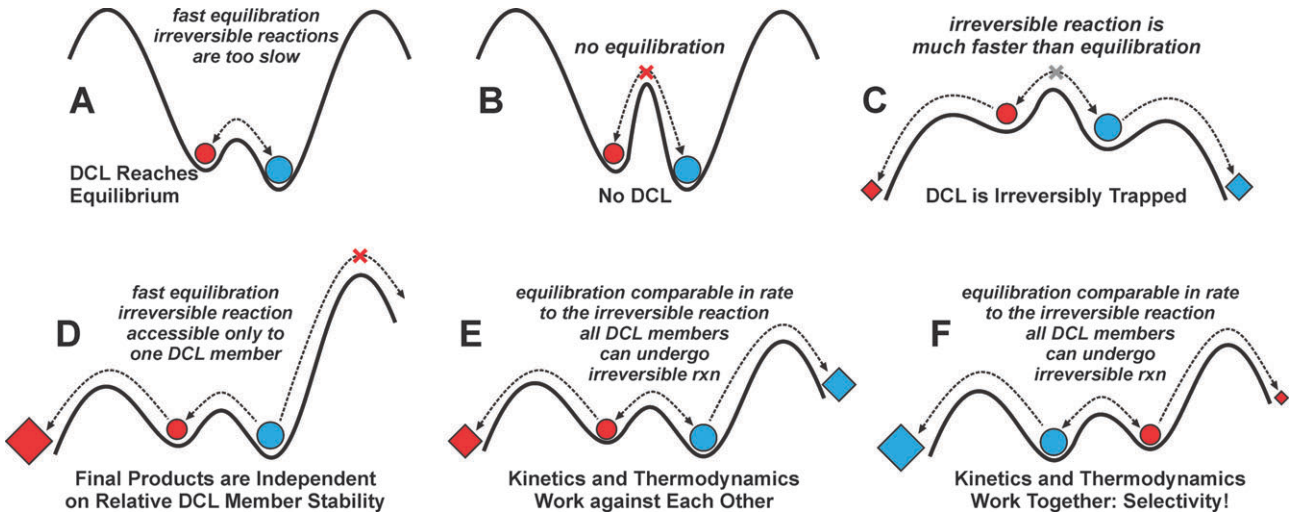


Fig. 1 Various combinations of kinetic and thermodynamic parameters lead to differing product distributions in DCLs. (A) DCL reaches an equilibrium in a case where barriers to the reversible equilibration reaction are low, and barriers to all side reactions are high. (B) In a non-dynamic library, compounds do not equilibrate because all barriers are too high. (C) In the case of irreversible trapping of a DCL, an irreversible reaction is much faster than the equilibration, and the DCL is "frozen," *i.e.* the distribution of irreversibly formed trapping products is the same as the original distribution of their precursors in the DCL. (D) If only one DCL component can irreversibly react, then selective production of its derivative should be expected, as the entire DCL will utilize that "escape route." In contrast, if multiple DCL components can irreversibly react, then their concentrations and relative reaction rates will play a role. (E) If one DCL member reacts quickly, but the other is more dominant at equilibrium, irreversible reaction is not expected to proceed selectively. (F) If a DCL member is more stable and also reacts quickly, then the irreversible reaction will express it to a greater extent than its equilibrium concentration would suggest. Circles denote compounds that are in formal equilibrium, with red being the less stable one. Squares signify irreversible reaction products derived from the circles of the same colour.

What happens when a rapidly equilibrating DCL is exposed to conditions in which one or more of its members can irreversibly react—and thus leave the DCL? The selectivity and product outcome will critically depend on the relative barriers to that irreversible reaction for all possible DCL members, and on the relative sizes of those barriers compared to the equilibration barrier. Fig. 1C–F illustrates four typical cases. In the first one (Fig. 1C), the barriers to the irreversible reaction have been symmetrically lowered; the irreversible reaction is very fast for all DCL members, and is also faster than the DCL equilibration. Thus, upon addition of the reagent that causes the irreversible reaction, members of the DCL will react quickly, not giving the library enough time to re-establish the disturbed equilibrium. In this case, the relative distribution of DCL components prior to the irreversible reaction will be faithfully captured in the relative distribution of the product of these irreversible reactions. This approach is of great practical value, as it converts DCL components into stable molecules that can be separated and analysed.

Three cases represented in Fig. 1D–F[11] highlight the situations in which barriers to the irreversible reaction have been unsymmetrically lowered. In the first case (Fig. 1D), irreversible reaction is accessible only to one DCL member (shown as the red circle in the "left valley"), and too slow for all other compounds in the DCL. In such a case, high selectivity in the irreversible reaction can be expected regardless of the stability and equilibrium concentration of its substrate. In essence, the reactive substrate simply "waits" for the equilibration to produce more of it, and even minor components of the library can be virtually quantitatively expressed from the DCL through this irreversible "escape route."

Two more complex cases are presented in Fig. 1E and F. Here, the irreversible reaction is accessible to both the "left" and the "right" compound, but with different barriers. In addition, both of these barriers are now comparable to the barrier for the DCL equilibration, and the selectivity here depends on the relative sizes of the three respective barriers. Shown in Fig. 1E is the case where the more stable compound (of which there is more at equilibrium) reacts with a lower $k_{\text{irreversible}}$, and the less stable compound reacts with a higher $k_{\text{irreversible}}$. Since the rates of the irreversible reaction depend also on the starting materials' initial concentrations, it is possible that both compounds react at comparable rates—and thus selectivity can be lost in this case where thermodynamics and kinetics work against each other. In contrast, Fig. 1F shows an example where the "blue" compound (in the left valley) is both more stable and faster-reacting, and this synergy of thermodynamics and kinetics can lead to high selectivities even in cases where all barriers are comparable in height.

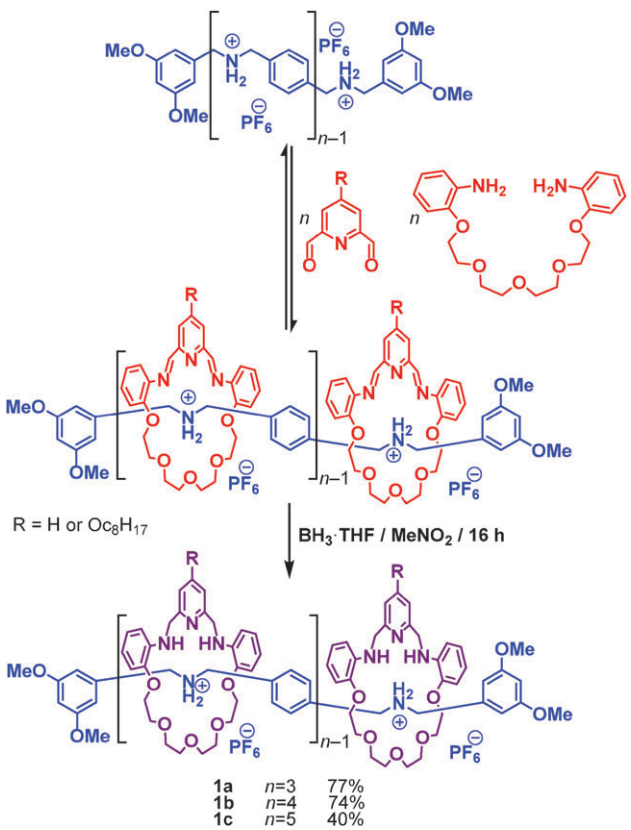
The remainder of this Tutorial Review will highlight selected examples of kinetically controlled phenomena operating on DCLs, with the intention of illustrating these energetic scenarios. We will begin with recent examples of DCL trapping through a fast irreversible reaction and then proceed to examples where kinetically controlled transformations of DCLs result in phenomena such as dynamic resolution, self-sorting and self-replication. Finally, we will describe examples of precipitation-induced organization of DCLs, where high

non-linear effects essentially kinetically overrule the thermodynamics of the DCL, and finish with a brief discussion of COFs: porous and potentially broadly useful materials produced through precipitation-driven DCC.

Trapping of DCLs through irreversible fixation

The dynamic nature of DCLs also represents a significant challenge during their separation and analyses, as dynamic species can decompose or interconvert during *e.g.* column chromatography. It is thus often necessary to "fix" the DCLs—that is, to effectively destroy their dynamic, interconverting character—in order to be able to manipulate and isolate individual DCL members. This fixation ideally needs to be irreversible and instantaneous, so that the DCL composition does not significantly change during the fixation process; conceptually, this corresponds to the rapid transformation of the energy profile shown in Fig. 1A into the one shown in Fig. 1C. There are two possible ways to achieve this: either the barrier to equilibration needs to be increased to the point that stops the exchange, or an irreversible reaction needs to be initiated at a rate which will dwarf that of the DCL equilibration. The fixation strategy depends on the nature of the chemical reactions involved in the DCL construction. Some reactions are dynamic only at high temperatures or in the presence of a catalyst. Fixation of such libraries is straightforward—as one only needs to lower temperature and/or quench the catalyst to stop the interchange. This situation is quite desirable, as the DCL does not chemically change during the fixation process. Examples include alkyne and alkene metathesis—where metal catalysts can be easily deactivated by *e.g.* filtration through silica, or transesterification and hydrazone exchange,[12] where changes in pH can completely shut down the exchange.

Some very prominent reversible reactions—imine metathesis, boroxine formation, acetal exchange—are not subject to this convenient control, as they proceed readily in the absence of a catalyst. With commonly used imine-based DCLs,[13] irreversible reduction of imines into amines can be quickly achieved with hydride reducing agents. Examples include Stoddart's synthesis of dynamic rotaxanes (Scheme 1). While imine metathesis could generate species as large as [11]rotaxane, irreversible reduction with BH_3·THF complex could cleanly produce only [3]-, [4]- and [5]rotaxanes **1a–c** in yields of 77%, 74% and 40%, successively. These decreasing yields highlight the absence of error-correction mechanisms in irreversible reduction: as side products accumulate, every subsequent reduction is less clean than the previous one.[14]

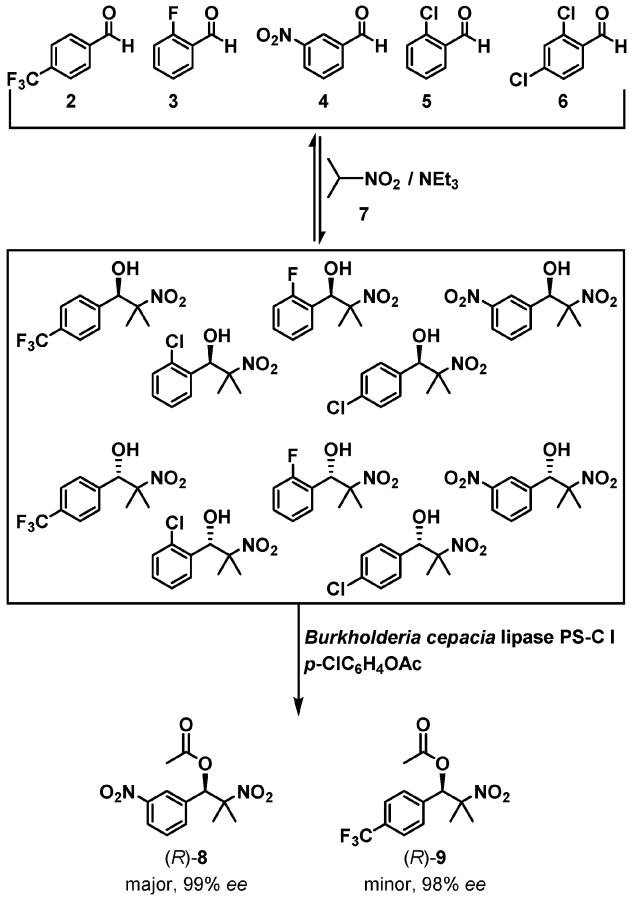


Scheme 1 Fixation of dynamically produced imine [*n*]rotaxanes through an irreversible reduction with BH_3·THF.

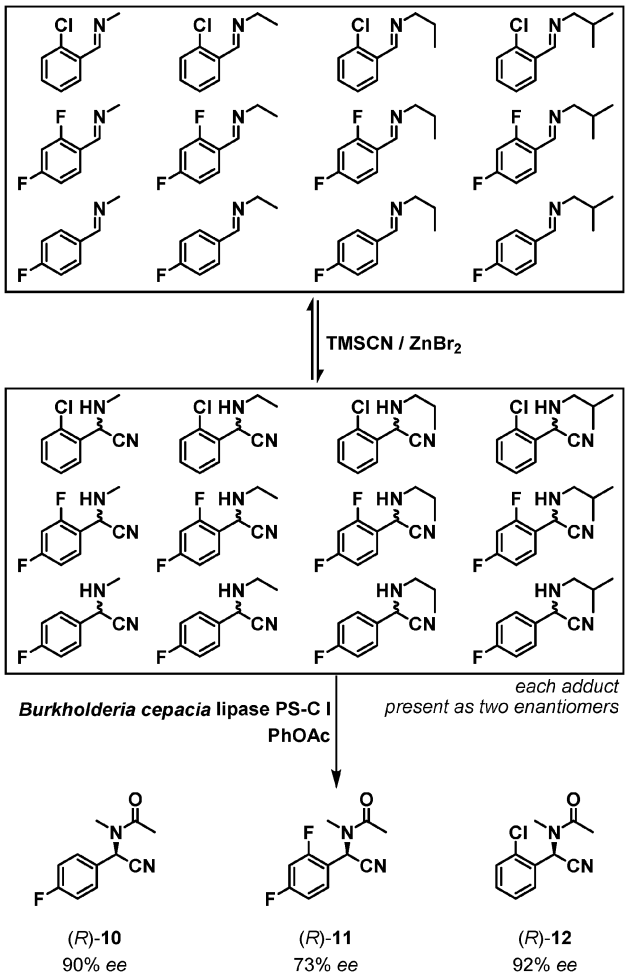
Dynamic chiral resolution of DCLs

Kinetic resolution represents one of the basic ways of obtaining enantiopure products from racemic starting materials. When a racemic mixture is allowed to react with a chiral reagent, the two enantiomers occasionally react at different rates. If these rates are sufficiently different, the fast-reacting enantiomer is fully converted into the product, while the leftover starting material contains only the less reactive enantiomer. The main disadvantage of this methodology is that 50% of the material—that is, the entire amount of the less reactive enantiomer—effectively gets wasted. In *dynamic kinetic resolution* protocols, the two enantiomers can equilibrate through *e.g.* epimerization. As the fast-reacting enantiomer leaves the mixtures, the less reactive enantiomer gets converted into its antipod and then reacts; in such cases, 100% of the racemic starting material can in principle be converted into a chiral product.[15] This kinetically-stipulated interconversion between the two enantiomers can be viewed as an elementary instance of DCC; energetically, it conforms to the situation represented in Fig. 1D.

In 2007, Ramström and coworkers have demonstrated that lipase enzymes can perform asymmetric resolution of much larger DCLs constructed through a reversible addition reaction. An equimolar mixture of aldehydes **2–6** (Scheme 2) was exposed to one equivalent of 2-nitropropane (**7**), to generate a DCL that contained five nitroaldol adducts, each present as two enantiomers. This library was subsequently exposed to *p*-chlorophenyl acetate (an acetylating agent), in the presence of *Burkholderia cepacia* PS-C I lipase. After two weeks, only two enantiopure acetylation products could be isolated: (*R*)-**8** (derived from **4**) was obtained in 53% yield, while (*R*)-**9** (derived from **2**) was produced in 33% yield. Both acetylated nitroalcohols were



Scheme 2 Dynamic lipase-catalysed asymmetric resolution of a DCL based on a nitroaldol reaction.



Scheme 3 Double kinetic chiral resolution of a dynamic library of Strecker adducts during irreversible enzymatic acetylation.

isolated with excellent enantiomeric excesses (ee) of >98%.[16] This protocol was afterwards optimized to produce individual acetylated nitroalcohols in yields as high as 92% and with 99% ee, starting from racemic starting materials.[17]

In a subsequent expansion of this protocol to the Strecker cyanation of imines, double kinetic resolution was observed, as the enzyme could independently select the best aldehyde and the best amine component. A DCL of 12 imines was constructed (Scheme 3, top) from three aldehydes and four amines. Reversible addition of the cyano moiety (through the reaction with TMSCN) onto the C=N bond introduced a chiral center, expanding the library to 24 Strecker adducts (Scheme 3, middle). The exposure of this DCL to *Burkholderia cepacia* lipase PS-C I, in the presence of phenyl acetate, resulted in the selective production of just three amides (*R*)-**10**, (*R*)-**11** and (*R*)-**12**, with ee's of 90%, 73% and 92%, respectively.[18] The yields of the three products amounted to just 65% of the total starting material mass balance, even after 40 d.

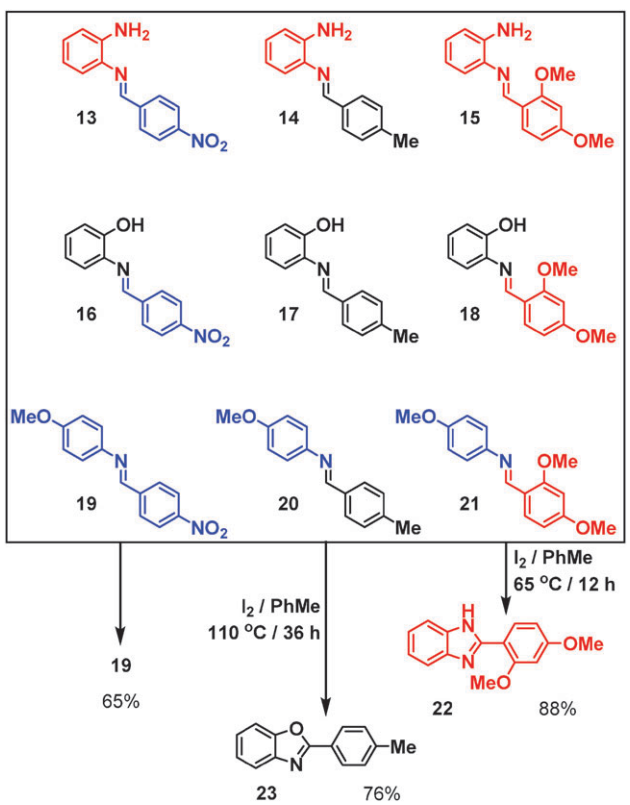
The same group also used this dynamic resolution methodology to identify the lipase's preferential substrates from the dynamic pools of cyanohydrins[19] and hemithioacetals.[20] Very recently, Ramström and coworkers showed that lipase-catalysed asymmetric resolution can also be achieved in a system which employed hemithioacetalization and nitroaldol reactions operating in parallel.[21] In the presence of *Burkholderia cepacia* PS-IM lipase, a single acetylated hemithioacetal product could be obtained from a library of six potentially competing precursors, with >90% ee and in 17 : 1 excess relative to the next most abundant product.

Kinetic self-sorting of DCLs

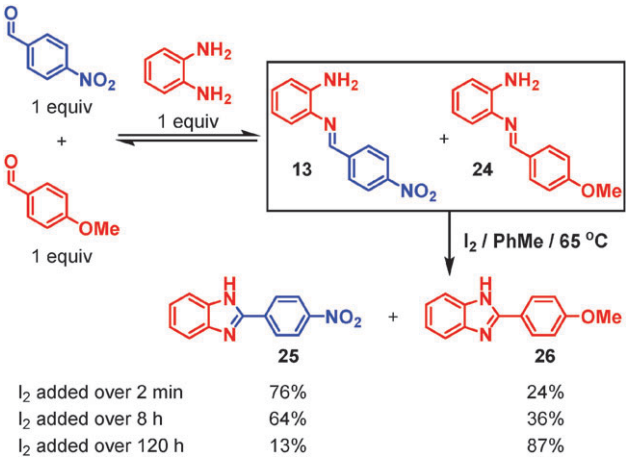
The dynamic kinetic resolution protocols described above utilized the reversibility inherent to DCLs to express the component that reacts the fastest in an asymmetric enzymatic acylation. During this process, all DCL members that shared a constituent with that fast-reacting species were sacrificed in order to create more of the enzyme's best substrate. We have recently developed an iterative (and non-enzymatic) version of this methodology, in which imine libraries constructed from *n* aldehydes and *n* amines spontaneously sort into just *n* pure imine products, which can be isolated in high yields. In this *self-sorting process*, dynamic resolution first isolates the fastest-reacting compound—at the expense of all other DCL members that share a constituent with it—and then moves onto the next

fastest-reacting compound in the smaller DCL that was the side product of the first resolution. This sequence iteratively repeats until no starting materials remain. While such self-sorting phenomena[22–24]—defined as the high-fidelity recognition of self from nonself—have been precedented until thermodynamic control,[25] our protocol was one of the first to proceed under dominant kinetic control. Conceptually, a self-sorting process represents an iterative application of selective reactivity depicted in the energy diagram shown in Fig. 1D.

Shown in Scheme 4 is a kinetically self-sorting system in which an irreversible imine oxidation reaction acts as the kinetic stimulus.[26] Within a 9-imine library **13**–**21**, compound **15** is the one most prone to oxidation because it contains the most electron-rich amine (1,2-phenylenediamine) and aldehyde (2,4-dimethoxybenzaldehyde) components. The oxidation conditions were initially kept mild—by employing relatively low temperature (65 °C) and a weak oxidant (I_2), whose concentration was kept very low by syringe pump addition—allowing the oxidation of only **15**. Because of the slow oxidation rate, the mixture had enough time to reequilibrate and produce more of **15**. As this process continued, imines in the library that shared either the aldehyde (**18** and **21**) or the amine (**13** and **14**) component with compound **15** were destroyed, and the electron-rich benzimidazole **22** was produced in 88% yield. In this case, the "self" from the above introduced definition of self-sorting includes all highly oxidizable components (shown in red in Scheme 4), which are able



Scheme 4 Self-sorting of a dynamic [3 × 3] imine library during the course of a slow, irreversible oxidation.

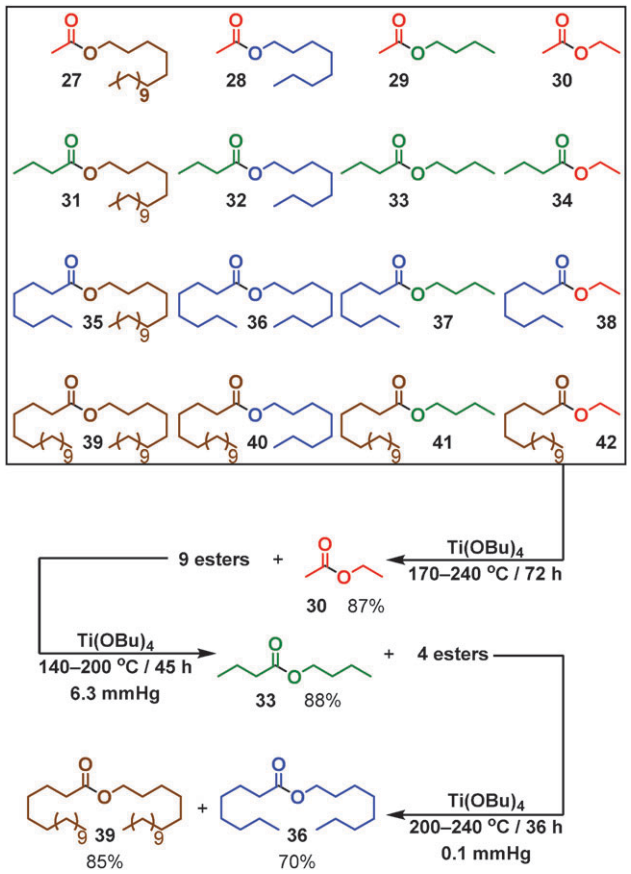


Scheme 5 Product distribution during the irreversible oxidation of a DCL depends dramatically on the rate of oxidant addition.

to distinguish themselves from the less readily oxidized members of the DCL (shown in blue and black).

Once this first oxidation was complete, the reaction temperature was increased, and the next electron-richest compound (**17**) was oxidized into its expected benzoxazole product **23**. By the same token, its oxidation disturbed the equilibrium and extracted the *o*-aminophenol and 4-methylbenzaldehyde components from all imines that contained them (**16** and **20**), yielding **23** in 76% yield. The sole remaining imine **19** could not be oxidized under these conditions and was isolated as such. In essence, a [3 × 3] library was self-sorted into three pure products under the combined influence of thermodynamic and kinetic parameters.

During our self-sorting oxidation experiments, an interesting apparent exception to the rule that the most electron-rich species are produced first was observed (Scheme 5). When 1 equiv. of 1,2-phenylenediamine was exposed to an equimolar mixture of 4-nitrobenzaldehyde and 4-methoxybenzaldehyde, imines **13** and **24** were formed. Imine **13** dominated at equilibrium because of the stabilizing push–pull effect. Slow oxidation of this small DCL, achieved over 8 h of iodine addition, resulted in the nitrobenzimidazole **25** as the main product (64 : 36). This was a surprising observation, but could be rationalized by the fact that the reaction rates depend not only on the relative oxidizabilities of the two imines (higher for **24**), but also on their relative concentration at equilibration (higher for **13**). This situation is illustrated in Fig. 1E, where the thermodynamic and kinetic parameters of an irreversible removal work against each other. In such a case, product distribution could be altered through the changes in the rate of oxidant addition: if I_2 was added instantaneously, the mixture was essentially frozen in the equilibrium state and **25** dominated the product mixture to the extent of 76 : 24. On the other hand, if the same oxidant was added over 5 d, the ratio inverted to 17 : 83, suggesting that the mixture was now given enough time to express **26** as the main product. While neither of these selectivities was synthetically very useful, they did suggest that an additional layer of control is possible through the variation of temporal distribution of external oxidants.

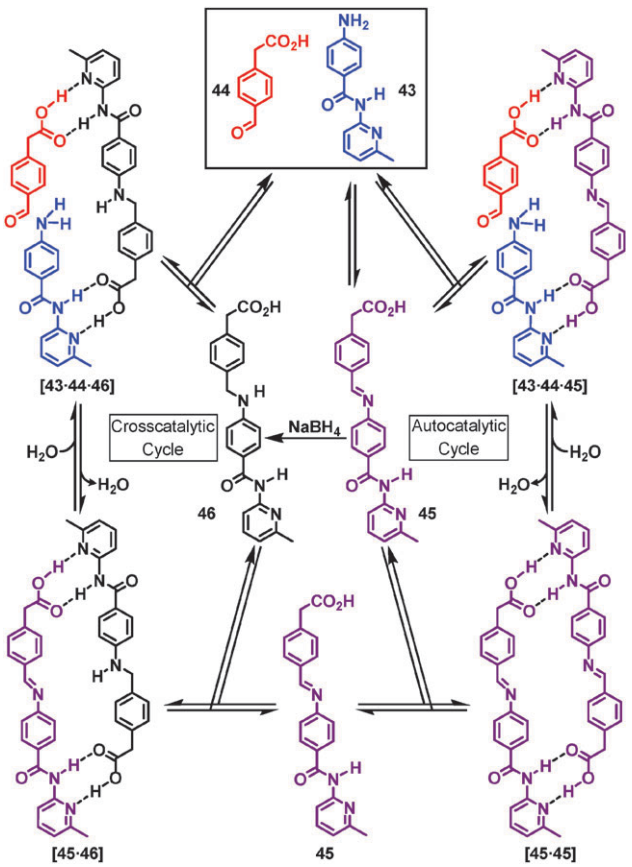


Scheme 6 Self-sorting of a [4 × 4] dynamic mixture of esters during a reactive distillation.

An irreversible stimulus for the self-sorting of DCLs does not have to be a chemical reaction. Physical transformations, such as the irreversible distillation of individual components of the mixture, can also be used to achieve simplification of complex DCLs into a handful of discrete high-purity products. We have shown[27] that dynamic imine libraries of up to 25 members could be reduced into just 5 pure products during the course of a vacuum distillation. The logic behind this process was identical to that demonstrated in Scheme 4: during the distillation of the most volatile imine, all other imines that shared either an aldehyde or an amine component with it were sacrificed to replenish that highly volatile imine as it was leaving the library. The process resulted in a high-yielding production of the most volatile imine and in a smaller residual DCL, from which this process was iteratively repeated. The same principle was recently demonstrated on the industrially more relevant dynamic ester libraries (Scheme 6).[28] Acyl exchange between the esters does not proceed spontaneously, so a metal alkoxide catalyst—NaO*t*-Bu or $Ti(OBu)_4$—was employed to ensure quick equilibration of the DCL. Distillation of such a freely interconverting library isolated first ethyl acetate **30**, sacrificing in the process all ethyl esters (**34**, **38**, **42**) and all acetates (**27**–**29**). Butyl butyrate **33** was isolated next at the expense of **31**, **32**, **37** and **41**. Final distillation step isolated **36** and left **39** as the distillation residue.[29]

Self-replication

One of the most fascinating properties of DCLs is self-replication.[30] This behaviour—wherein a molecule facilitates the creation of an exact copy of itself, leading to non-linear amplification of its production rate—is one of the essential properties of living systems, and attempts to replicate it in a fully synthetic context are clearly of interest in the studies of the chemical origin of life.[31] Philp's group has been particularly active in integrating self-replication with DCC and identified two main scenarios that can lead to self-replication. In the first approach, one of the DCL components catalyses its production from other library members and its concentration quickly increases until the final equilibrium distribution is reached. An example of this strategy is shown in Scheme 7.[32] Imine **45** can be produced from its precursor aldehyde **44**—which is equipped with a carboxylic acid recognition site, and amine **43**—which bears an amidopyridine recognition motif. Once formed, imine **45** is capable of organizing its precursors **43** and **44** into a ternary complex [**43**·**44**·**45**]. Within this complex, **43** and **44** can react in a pseudo-unimolecular fashion, rapidly producing another copy of template **45** and completing the self-replication sequence. Autocatalytic behaviour was confirmed by

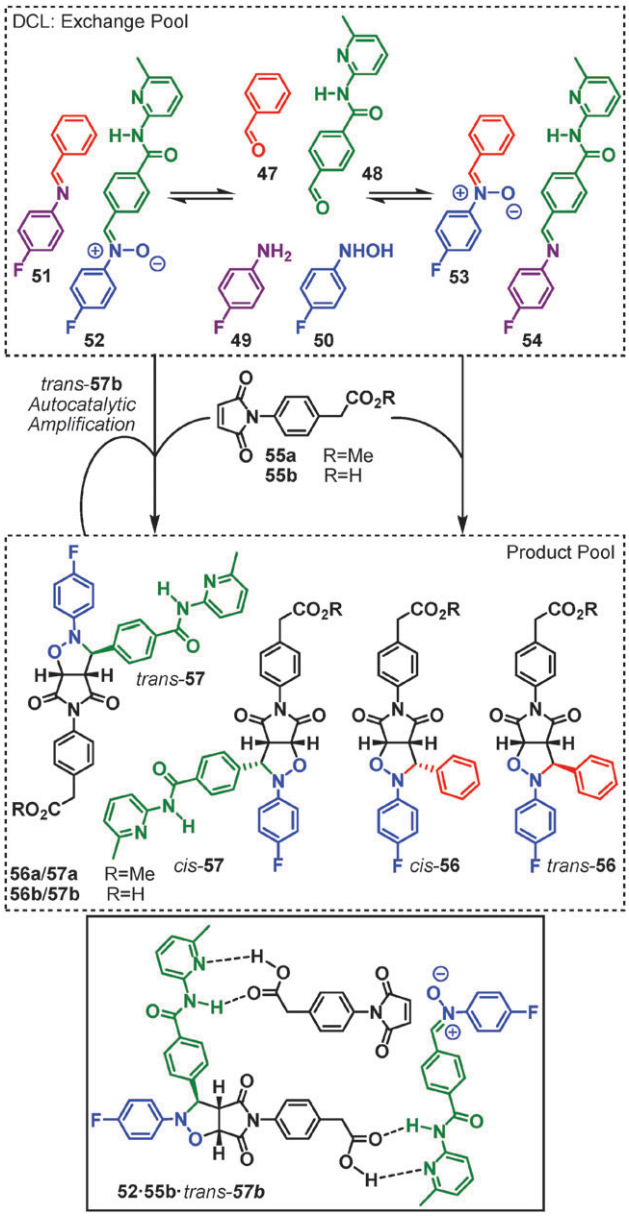


Scheme 7 Self-replicating imine **45** is capable of organizing its precursors **43** and **44** into a ternary complex, thus greatly accelerating the rate of its own formation. The reduced product **46** also acts as an efficient cross-catalyst for the production of **45**.

independent experiments in which a small amount of **45** was added to the mixture at the onset of the reaction, resulting in a significant increase in the initial reaction rate.

While this self-replication strategy leads to rapid and non-linear acceleration of the production of self-replicator **45**, the maximum producible amount of **45** is fundamentally limited. This limitation stems from the fact that **45** remains in equilibrium with its starting materials; since no irreversible reaction is involved (Fig. 1A), the position of that equilibrium depends only on the relative thermodynamic stabilities of the involved species, and autocatalysis does not change that distribution—it only ensures that equilibrium is reached faster. In other words, equilibrium constant and free energy are both state functions, meaning that they are independent on the pathway or the rate at which the equilibrium state was reached. In order to liberate self-replication processes from these restriction imposed by equilibria, an irreversible kinetically controlled step is needed. This problem was partially overcome by the *in situ* irreversible reduction of **45** into secondary amine **46**. Compound **46** could still organize **43** and **44** into a cross-catalytically competent ternary complex [**43**·**44**·**46**], but **46** no longer equilibrated with **43** and **44**. In this cross-catalytic cycle, imine **46** proved to be a better catalyst for the creation of imine **45** than **45** itself.

In an alternative kinetically controlled approach, a DCL component reacts irreversibly to form a product which then catalyses its own formation. This situation can energetically correspond to any of the three scenarios described in Fig. 1D–F, since non-linear amplification of the autocatalytic species can override *e.g.* unfavourable thermodynamics of the precursor mixture. Since this irreversibly formed material is not a member of the DCL, it no longer equilibrates with the rest of materials and can express itself in high yields and selectivities relative to all other species. Philp and coworkers demonstrated this kind of self-replication in a mixed imine/nitrone DCL shown in Scheme 8.[33,34] Starting with aldehydes **47** and **48**, 4-fluoroaniline (**49**) and *N*-(*p*-fluorophenyl)hydroxylamine (**50**), a small DCL composed of two imines (**51** and **54**) and two nitrones (**52** and **53**) was constructed. In two separate experiments, this DCL was exposed to maleimides **55a** and **55b**, which were capable of irreversibly reacting with nitrones in a 1,3-dipolar cycloadditions, but not with imines. When maleimide **55a** was used, four cycloaddition products were obtained (**56a** and **57a**, both generated as a mixture of the *cis*- and the *trans*-adducts) with rather low selectivity. However, when dipolarophile was switched to compound **55b** substituted with the free carboxylic acid group, the *trans*-**57b** cycloadduct could template its own formation through complementary hydrogen bonding with precursor nitrone **52** and maleimide **55b**. The formation of a reactive ternary complex [**52**·**55b**·*trans*-**57b**] resulted in a 100-fold acceleration of this reaction, and after 16 h, self-replicating adduct *trans*-**57b** constituted more than 80% of the product pool. Autocatalytic behaviour was confirmed through control experiments in which the mixture of **53**, **54** and **55b** was seeded with a small amount of *trans*-**57b**, resulting in a large initial rate increase. None of the three alternative cycloadducts could catalyse their own formation.

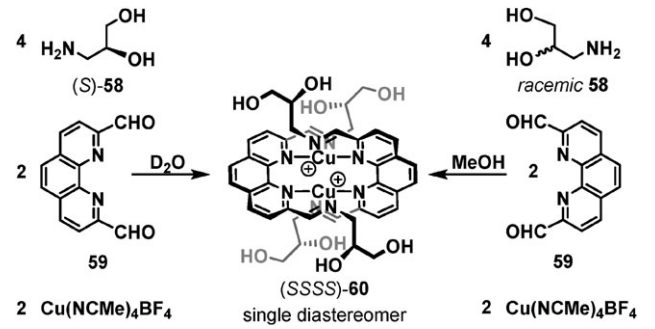


Scheme 8 Self-replication of the irreversibly produced cycloadduct *trans*-**57b** from a DCL containing its precursor nitrone **52**. Shown in the box on the bottom is the ternary complex [**52**·**55b**·*trans*-**57b**] involved in the autocatalytic cycle.

Dynamic combinatorial self-replication of large length scale self-assemblies was recently reviewed by Giuseppone.[35,36]

Precipitation-driven self-sorting

Kinetically controlled transformations of DCLs are not confined to a single phase, *i.e.* dilute solution.[37] Precipitation or crystallization of DCL components is often either spontaneous, or can be easily induced by *e.g.* changes in solvent composition. The resultant solid–liquid mixture is, in principle, still subject to the same reversible reaction(s) that operate in the solution; in other words, solution and the precipitate should be in



Scheme 9 Spontaneous resolution of a twelve-component helicate DCL into a single diastereomer of **60** (present as both enantiomers).

equilibrium. However, at least two factors make this assumption quite unrealistic in most systems: (a) in the cases of bulk precipitation, only a small portion of the precipitate on the surface is in effective contact with the solution, and (b) as a seeding event, precipitation is subject to large non-linear effects, while dissolution (*i.e.* precipitation's obverse) is not. Realistically, while the exchange between the solution and the precipitate still occurs, it is typically orders of magnitude slower than the exchange between the species that remain in the solution. With such very different kinetics, the precipitation of species from the DCL can be considered as essentially irreversible sequestration, fitting the scope of this review (and, because of non-linear amplification effects, again corresponding to either of the three situations shown in Fig. 1D–F).

Nitschke *et al.* have shown[38] that a dynamic library of diastereomeric imine-copper helicates spontaneously collapses into a single diastereomer upon crystallization (Scheme 9). When enantiopure amine (*S*)-**58** was mixed with aldehyde **59** in the presence of Cu^+ source, a single helicate (*SSSS*)-**60** was formed, wherein all amine components have the same chiral configuration. However, when compound **58** was employed as a racemic mixture, helicate **60** was formed as a mixture of all twelve possible stereoisomers (six diastereomers, each present as both enantiomers). Crystallization of this mixture from a MeOH solution (over two weeks) resulted in X-ray quality single crystals, which revealed only (*SSSS*)-**60** (and its enantiomer (*RRRR*)-**60**) and no evidence of any of the other diastereomers. As the imine exchange and copper coordination are both reversible, the DCL could trade the materials to amplify the least soluble diastereomer, effectively self-sorting the two enantiomers into two enantiopure assemblies.

Stoddart's group has masterfully used fractional precipitation to isolate fascinating interlocked molecules. During crystallization, a dynamic library consisting of aldehyde, amine and metal ion precursors was shown to produce either Borromean rings[39] (interlocked assemblies of three macrocyclic rings, neither pair of which is mutually interlocked) or Solomon knots, consisting of two doubly interlocked macrocycles. While both interlocked species could be observed in the solution, judicious choice of crystallization solvent and/or templating metal resulted in the isolation of just a single product.[40]

Recently, our group has shown that dynamic imine libraries of as many as nine members spontaneously self-sort into three pure compounds during the course of slow precipitation from EtOH–H_2O mixtures.[41]

Covalent organic frameworks

Among the precipitation-driven protocols for the simplification of DCLs into a single species, syntheses of *covalent organic frameworks* (*COFs*)[9] stand out, as they produce extended materials, rather than small molecules (or collections of small molecules). COFs are two- or three-dimensional polymeric materials formed through DCC: reversible reactions between one or more oligofunctional precursors proceed until an extended ("infinite") structure of an insoluble polymer is formed. Because of their modular synthesis, crystallographic order and high thermal stability, COFs have been proposed as platforms for light harvesting, gas storage and separation, catalysis, as well as components of electronic devices.

First examples of COFs were prepared by Yaghi's group in 2005,[42] and were based on dynamic boroxine and catechol/boronate ester linkages (Fig. 2). Even in this early work, it was realized that the slow removal of water is essential for the error-correction process that results in well-defined crystalline materials. Subsequently, Dichtel *et al.* utilized a $BF_3{\cdot}Et_2O$-catalysed deprotection of catechol acetonides to prepare COFs based on phthalocyanine boronate esters.[43] The same group also performed one of the rare mechanistic investigations of the generation of COFs (Scheme 10).[44] As the BF_3-mediated deprotection of the catechol acetonide (**61**) yields free catechol, boronic acid **63** is reversibly trapped in two reservoirs: either in its boroxine **62** or within adduct $BF_3{\cdot}$**63**. Even though both equilibria disfavour free boronic acid, its effective sequestration within the insoluble COF forces the slow release of **63** from these reservoirs. As the COF molecule grows bigger, other exchange processes also start playing a role. Using model small molecules, Dichtel's group elucidated relative rates of those dynamic reactions. Two boronate esters will quickly swap their catechol and boronic acid moieties in the presence of catalytic amounts of H_2O, and a boronate ester will also quickly exchange with an external catechol. On the other hand, exchange of a boronate ester with a free boronic acid is much slower.

While boron-based COFs initially dominated the field, in recent years other dynamic functional motifs based on *e.g.* imines[45] and hydrazones[46] have been introduced into COF structures. All of these materials were produced as microcrystalline powders and analysed by powder X-ray diffraction; their computationally predicted structures were then correlated with the obtained diffraction patterns and—if the two agreed—a structure was assigned. The inability to produce large crystals that would have allowed direct structure assignment *via* single crystal X-ray diffraction was viewed as a kinetic problem. In order to produce large crystals, the rate of crystal growth must be slower than the rate of the exchange reaction, and the kinetics of most employed dynamic reactions was too slow (at least at the solution/precipitate interface) to allow efficient error-correction needed for the growth of single crystals.

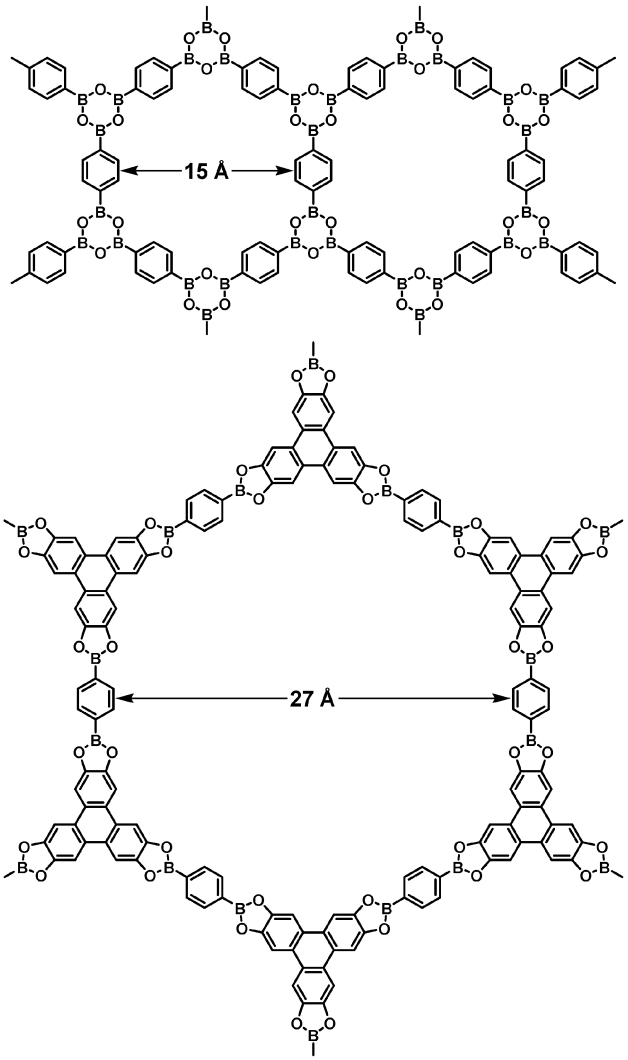
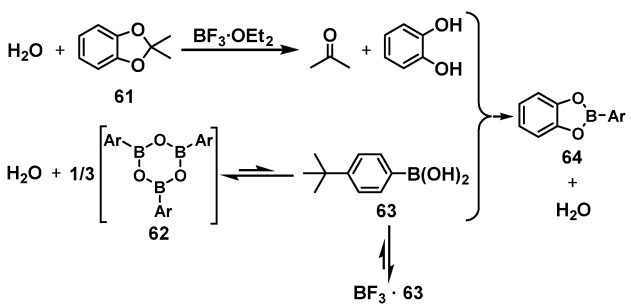
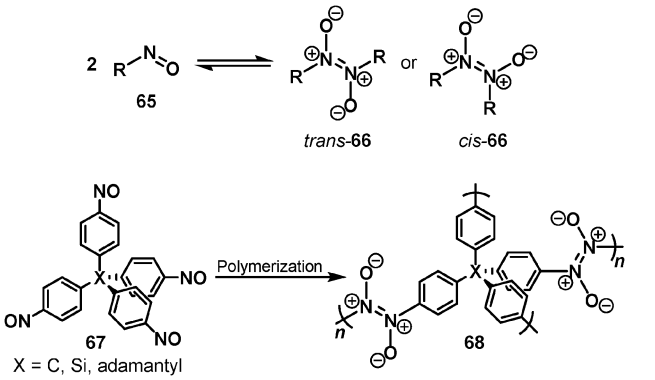


Fig. 2 Repeating units of COFs can be based on the reversibly formed boroxine units (top) or boronate esters (bottom), among other structural motifs.



Scheme 10 Modelled mechanism of formation of boronate ester-based COFs from catechol acetonide precursors.

Very recently, Wuest *et al.* have shown[47] that the reversible formation of azodioxides (**66**, Scheme 11) from nitroso compounds **65** has a low enough activation barrier (20–30 kcal mol^{-1}) to allow the growth of large crystals. This insight resulted in the synthesis and characterization of first single-crystalline COFs: starting from



Scheme 11 Exchange between nitroso compounds and their azodioxide dimers is facile enough to permit slow crystal growth necessary for the formation of single-crystalline COFs **68**.

rigid tetrahedrally substituted precursors **67** (Scheme 11, bottom), thermal polymerization resulted in COFs **68**.

Conclusions

This Tutorial Review highlighted some of the directions in which the kinetically controlled chemistry of DCLs is developing. The introduction of an irreversible reaction step into otherwise dynamic systems allows the isolation of stable, robust molecules and materials, as well as their facile characterization. At the same time, these kinetically controlled protocols still profit from the underlying thermodynamic reversibility, as DCL members can freely trade material—and, in turn, information[48]—among themselves as they progress through the irreversible reaction.

The nascent areas discussed in this review use well-understood combinations of kinetic and thermodynamic parameters to achieve selective syntheses of discrete and stable products, starting from complex (“messy”) mixtures of precursors. Their success once again highlights the importance of studying physicochemical parameters of reactions commonly used in synthesis, and the multi-layered relationship between kinetics and thermodynamics. Not all aspects of this relationship have been discussed here; for example, the rate at which different components of a DCL interconvert can greatly vary and thus each DCL likely has more and less dynamic subsets. If sufficiently well known, these and other intricacies of DCLs could all be synthetically exploited. In our view, the complex interconnections between kinetic and thermodynamic parameters of a system represent an opportunity—rather than a nuisance—for synthetic chemistry. Taking the long view, intricate understanding of parameters that guide behaviours of dynamic mixtures could contribute to our ability to “dial in” the desired product by the appropriate choice of *e.g.* temperature, external reagent, rate of that reagent’s addition and other parameters. Research on complex libraries of interacting compounds offers unique opportunities to discover system-level properties,[48] which by their very definition cannot be observed by working on compounds in isolation.

Significant challenges remain in the area of dynamic combinatorial chemistry as a whole. Probably the most problematic is the relatively small pool of well-behaved reactions that are reversible, and whose reversibility can be shut down through a convenient ''fixation.'' Most acutely, reversible C–C bond forming reaction still number in single digits. A major breakthrough would be the discovery of reverse versions of Pd-catalyzed C–C couplings that revolutionized synthetic chemistry of the past three decades. This problem is partially cultural: scientists working on DCC and reaction discovery rarely collaborate or attend the same conferences. As a result, the development of a new reaction is often abandoned once it is established to lead to equilibria or product mixtures—even though such reactions might very well be useful in thermodynamically controlled procedures.

Additionally interesting would be the development of reactions whose dynamic behaviour could be conveniently turned ON or OFF (by *e.g.* light), or possibly even scaled along the continuum,[49] so that a large DCL could be fully or partially frozen at will.

Nature seems like an ideal playground for dynamic combinatorial chemistry. It offers a virtually limitless diversity of highly complex molecular mixtures. If such libraries could be made dynamic, and then channelled in ways which would allow the selective synthesis of discrete materials—even in a primitive, non-enzymatic sense—many new advances in sensing, biomass conversion and environmental applications could be expected.

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