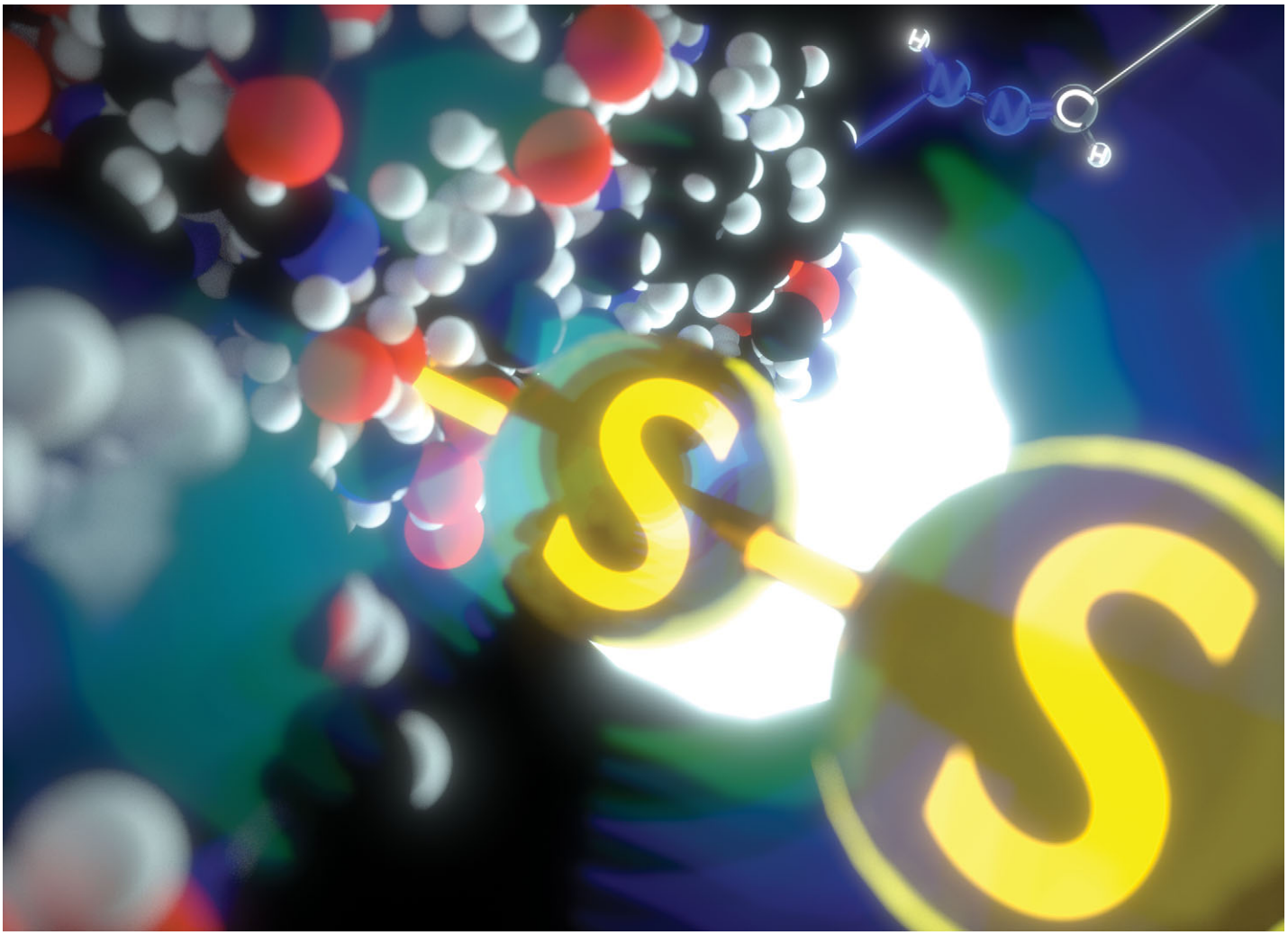

Featuring work from the Matile group at the University of Geneva, Switzerland.

Functional systems with orthogonal dynamic covalent bonds

The simultaneous use of more than one type of dynamic covalent bond – surprisingly rare and recent – is shown to provide access to otherwise challenging topics, including molecular systems that can not only bind, transport or transform but also self-sort, self-heal, adapt, replicate, transcribe, or even walk and "think".

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Functional systems with orthogonal dynamic covalent bonds

Adam Wilson, Giulio Gasparini and Stefan Matile*

This review summarizes the use of orthogonal dynamic covalent bonds to build functional systems. Dynamic covalent bonds are unique because of their dual nature. They can be as labile as non-covalent interactions or as permanent as covalent bonds, depending on conditions. Examples from nature, reaching from the role of disulfides in protein folding to thioester exchange in polyketide biosynthesis, indicate how dynamic covalent bonds are best used in functional systems. Several synthetic functional systems that employ a single type of dynamic covalent bonds have been reported. Considering that most functional systems make simultaneous use of several types of non-covalent interactions together, one would expect the literature to contain many examples in which different types of dynamic covalent bonds are similarly used in tandem. However, the incorporation of orthogonal dynamic covalent bonds into functional systems is a surprisingly rare and recent development. This review summarizes the available material comprehensively, covering a remarkably diverse collection of functions. However, probably more revealing than the specific functions addressed is that the questions asked are consistently quite unusual, very demanding and highly original, focusing on molecular systems that can self-sort, self-heal, adapt, exchange, replicate, transcribe, or even walk and "think" (logic gates). This focus on adventurous chemistry off the beaten track supports the promise that with orthogonal dynamic covalent bonds we can ask questions that otherwise cannot be asked. The broad range of functions and concepts covered should appeal to the supramolecular organic chemist but also to the broader community.

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1 Introduction

The creation of functional systems from scratch is a central objective in organic chemistry. Covalent, non-covalent and dynamic covalent bonds[1–3] are available as tools for the construction of such

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Adam Wilson

Adam Wilson received his PhD in 2012 working in the group of Prof. David Leigh. His thesis explored the use of rotaxanes as molecular machines, demonstrating the transport of a macrocycle in either direction along a rotaxane thread by the use of a chiral organocatalyst. In 2012 he moved to the group of Prof. Stefan Matile in the University of Geneva, where his current research is on anion–π interactions and their application in catalysis.

Giulio Gasparini

Giulio Gasparini obtained his PhD in 2008, working in the group of Prof. Paolo Scrimin and Prof. Leonard J. Prins. His thesis was based on the discovery of new catalysts using dynamic covalent capture and the development of new methodologies for library screening. After a period studying triphenolamine adducts as chiral catalysts in the group of Prof. Giulia Licini, he moved to Geneva to work in the group of Prof. Stefan Matile. His current research topic focuses on poly(disulfide) polymers as cell-penetrating vectors.

non-covalent	dynamic covalent	covalent
hydrogen bonds	disulfides	C-C
ion pairs	hydrazones	C-H
hydrophobic	boronic esters	C-O
π-π	imines	C-N
cation-π	thioesters	C-S
		C-P
		C-B
anion-π	hemi-/acetals	O-H
halogen bonds	hemiaminals	O-N
dipole-dipole	hemithioacetals	O-S
ion-dipole	dithianes	O-P
...	α-aminonitriles	O-B
	nitrones	...
	alkenes	
	enones	
	nitroolefins	
	...	

Fig. 1 In supramolecular functional systems, dynamic covalent bonds can combine the advantages of non-covalent and covalent bonds. The most popular members of each class are listed first, whereas promising and in part just emerging alternatives appear below the dashed line.

"active" molecular or supramolecular architectures (Fig. 1). The importance of both covalent and non-covalent bonds is well appreciated. Among non-covalent interactions, hydrogen bonds, ion pairs, hydrophobic interactions, π–π interactions and cation–π interactions[4] can be named as the basic set. The expansion of this surprisingly limited toolkit attracts much current scientific attention. Leading examples include anion–π interactions[5–7] and halogen bonds,[8,9] the underrecognized counterparts of cation–π interactions[4] and hydrogen bonds, respectively.

The interest in dynamic covalent bonds may be seen as having originated from the same desire to discover new tools for the creation of function. Dynamic covalent bonds are unique in the sense that they combine the characteristics of covalent and non-covalent bonds.[1–3] Under certain conditions, they can reversibly form and break like non-covalent bonds. Under different conditions, they can be as strong and permanent as covalent bonds. The disulfide bond, for example, is stable under neutral and acidic conditions, but under reductive or basic conditions in the presence of thiolates, disulfides exchange rapidly. Hydrazones are stable under neutral and basic conditions but readily hydrolyze under acidic conditions and exchange in the presence of hydrazides, aldehydes or ketones. Boronic esters are less stable. They hydrolyze quite easily and exchange in the presence of vicinal diols and catechols. Imines, the less stable homologs of hydrazones, are obtained from amines and aldehydes or ketones. Like disulfides, thioesters exchange rapidly with thiols.

Beyond these top five, there exists a rich collection of less frequently used dynamic covalent bonds, each with its own specific characteristics. Efforts to apply dynamic covalent bonds such as hemiacetals,[10] thiohemiacetals[11] or dithianes[12] in functional systems are ongoing. This review will also cover examples using aminonitriles,[13] alkenes that equilibrate with Cope rearrangements[14] and chirality sensors employing hemiaminals.[15] It is also important to emphasize that a certain grey area exists in the definition of the dynamic covalent bonds. The term may be extended to include many bonds that one would normally call covalent, but that become labile under particular, highly specific conditions.

The dual nature of dynamic covalent bonds offers unique advantages for the creation of function. The recent, rapid growth of dynamic covalent chemistry has provided many wonderful examples, the most visible of which is their use in dynamic covalent libraries.[1–3] These libraries are composed of mixtures of cyclic and linear oligomers with rapidly exchanging subcomponents. The presence of templates can shift their composition toward a desired distribution. In contrast to most supramolecular systems assembled with non-covalent bonds, active structures arising from templated dynamic libraries can usually be purified and isolated under conditions that do not permit further equilibration.

The recent progress with dynamic covalent libraries confirms that dynamic covalent bonds are ideal tools for generating diversity and exploring the possibilities of templation and substrate-induced amplification. Dynamic covalent bonds further excel when used in challenging topics such as self-repair, self-healing, adaptive self-sorting, replication and transcription, often operating with proximity effects and sometimes leading to highly sophisticated multicomponent architectures.[1] Many elegant applications of these advantages to create functional systems with single dynamic covalent bonds exist, from catenanes that bind acetylcholine[16] to enzyme inhibitors or sensors of the heterogeneity of lipid bilayer membranes.[17]

Lessons from nature provide superb examples of how dynamic covalent bonds may be used in functional systems. Disulfide exchange during protein folding is arguably the most impressive illustration of dynamic covalent bonds at work in biology, beautifully exploited in daily life by the hairdresser.[18] The same chemistry accounts for many of the properties of rubber.[18] In addition, thioester exchange is employed to perfection in polyketide biosynthesis,[19] dynamic imines are essential in the chemistry of vision, dynamic enone chemistry ensures that hot spices feel really hot,[20] hemiacetal chemistry is not limited to sugars but also plays an important role in membrane-active natural products such as amphotericin, nystatin or monensin, and so on.

Stefan Matile

Stefan Matile was educated at the University of Zurich (PhD 1994, with Wolf Woggon) and Columbia University (1994–1996, with Koji Nakanishi). In 1996, he joined the faculty of Georgetown University, Washington DC, as an assistant professor. Three years later, he moved to the University of Geneva, where he is currently a Full Professor in the Department of Organic Chemistry and the National Centre of Competence in Research (NCCR) in Chemical Biology, and an ERC Advanced Investigator. His research focuses on synthetic supramolecular multicomponent architectures and their use as ion channels, photosystems, sensors and catalysts.

In functional systems, non-covalent bonds are routinely used together. For example, the self-assembly of DNA duplexes involves a combination of hydrogen bonding, π–π interactions, hydrophobic interactions and charge repulsion. The orthogonality of hydrophobic interactions and hydrogen bonding, increasing and decreasing with increasing polarity of the environment, respectively, is of particular importance for the function of double-stranded DNA. All principal non-covalent interactions contribute to protein secondary and tertiary structures, and the design of synthetic functional systems is inconceivable without the insightful combination of orthogonal non-covalent bonds. One might thus assume that the use of orthogonal dynamic covalent bonds would be commonplace in synthetic functional systems. Surprisingly, quite the opposite is true. Only a few examples presently exist in the literature. In sharp contrast to this rare combination of two or more dynamic covalent bonds, dynamic covalent bonds are routinely used together with non-covalent bonds. Sequence-adaptive thioester peptide nucleic acids (PNAs) discussed in the following can serve as a telling example for this approach to generate function.[21] Coordination to metals is also very frequently used in combination with dynamic covalent bonds.

The concept of orthogonality has already appeared in a number of reviews with emphasis on the combination of dynamic covalent bonds with coordination chemistry or in the general context of reactivity and supramolecular interactions.[22–24] However, compelling experimental support of the concept of organic orthogonal dynamic covalent bonds is very rare and recent. The following will comprise a brief summary of structural studies that demonstrate the scope and applicability of orthogonal dynamic covalent chemistry, followed by a review of functional systems with orthogonal dynamic covalent bonds. Hopefully, these illustrations will stimulate the more frequent use of orthogonal dynamic covalent bonds to create function.

2 Orthogonal dynamic covalent bonds

The concept of orthogonality of dynamic covalent bonds first appeared in 2001 in combination with coordination to metals.[25] In 2005, two true, *i.e.*, organic, orthogonal dynamic covalent bonds were placed for the first time in dynamic libraries.[26] In this study, disulfide exchange produced acyclic or cyclic oligomers, whereas thioester exchange capped the acyclic oligomers and prevented cyclization. The longest oligomer in a mixture of at least eight molecules was found to be compound **1** (Fig. 2). Three years later, a similar study was published, focusing on disulfides and hydrazones.[27] A simple molecule equipped with a disulfide bond and two hydrazides was used. By exposing this molecule to an aqueous solution containing both aldehydes and thiols, hydrazone or disulfide exchange could be turned on and off simply by changing the pH (2.5 and 8.5, respectively). Moreover, the authors were able, using intermediate pH (4.5) and in the presence of a catalyst (aniline), to force both moieties to undergo dynamic exchange simultaneously, albeit at a lower rate. They also pointed out that the system reached different product distributions depending on the order of activation of the two exchange reactions.

A similar approach was used in a study published back-to-back with this report. Here, a building block carrying both a protected aldehyde and a disulfide bond was introduced to study the exchange of thiols and hydrazides at different TFA/TEA ratios.[28] The results confirmed that the two chemistries could be merged, opening the field of dynamic libraries in which the two exchange processes can be carried out sequentially and repetitively. In a follow-up study, a dynamic combinatorial library containing three different exchangeable motifs – hydrazones, disulfides and thioesters – was introduced.[29] While the hydrazones were dynamic in the presence of a catalytic amount of acid, the disulfides and thioesters only underwent exchange simultaneously under basic catalysis. The dynamic covalent library was generated by exposing a building block, containing both a disulfide bond and an aldehyde, to an excess of two different hydrazides, a thioester and a free thiol. Two different exchange protocols were used. In the first, hydrazone exchange in acidic conditions was followed by thiol–thioester exchange on the addition of an excess of base. In the second, the library was first exposed to base and then an excess of acid was added. The final compositions of the dynamic combinatorial library obtained using the two different chemical pathways were again

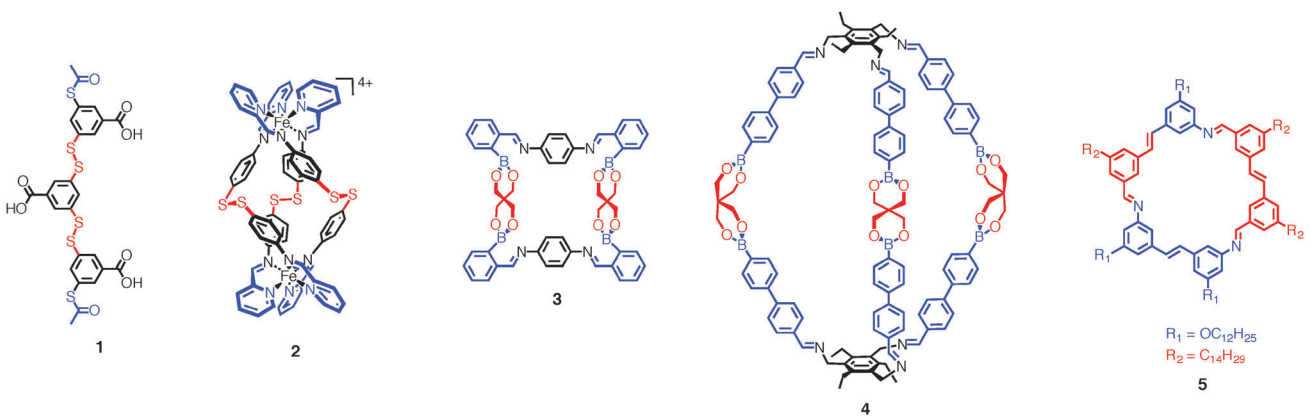


Fig. 2 Early and advanced architectures with orthogonal dynamic covalent bonds.

different, due to the fact that product distributions can be shifted away from the one corresponding to the overall energy minimum.

The first application of orthogonal dynamic covalent chemistry in a functional system, an NMR shift reagent based on imines and boronic esters, was presented in a memorable departmental lecture by Tony James in Geneva on 18 January 2007.[30,31] This breakthrough inspired the construction of multicomponent architectures with orthogonal dynamic covalent bonds in the group of Jonathan Nitschke, then in Geneva;[32,33] it also led to the use of orthogonal dynamic covalent bonds in porous biosensors in the Matile group (see below).[34] The same year, Otto and Nitschke reported the triple helix **2**, combining orthogonal dynamic disulfide and imine bonds with coordination to iron.[32] Soon after, the Nitschke group also reported metal-free architectures constructed from imines and boronic esters, including macrocycle **3**.[33] From there, the chemistry of multicomponent architectures with orthogonal dynamic covalent bonds was advanced to a very high standard by the group of Kay Severin in Lausanne.[35–37] The giant macrobicycle **4** is just one of many marvelous structures reported over the years.

Most recently, macrocycles of different shapes and sizes have been synthesized using two different orthogonal dynamic covalent reactions, *i.e.*, imine and olefin metathesis.[38] For this study, a small collection of vinyl anilines and vinyl benzaldehydes was used. The synthesis of macrocycles such as **5** was tried by simply mixing these compounds in the presence of TFA (trifluoroacetic acid; to improve imine exchange) and Grubbs–Hoveyda second-generation catalyst. Unfortunately, even if the conversion was higher than 95%, polymeric species predominated. Good results were obtained by running the two different reactions in sequence, *i.e.*, imine metathesis followed by olefin metathesis. The amines and aldehydes were allowed to react until the imine formation was complete; then Grubbs–Hoveyda catalyst was added to the system, giving the desired macrocycles in good yield. Following this procedure several different macrocycles were synthesized, their size and shape tuned simply by selecting the appropriate building blocks.

These are just a few examples of structural studies with orthogonal covalent dynamic bonds. However, there are not many more in the literature. In the following, the use of orthogonal dynamic covalent bonds to build systems with interesting functions will be described in more detail. This summary is almost comprehensive because the literature is not very rich on this topic: the field is in its early stages and hopefully will grow in the future.

3 Functional systems with orthogonal dynamic bonds

3.1 Molecular motion

The molecular "walkers" developed by the Leigh group are one of the most impressive examples of orthogonal dynamic covalent bonds in action (Fig. 3).[39] The objective is to move a molecular component along a molecular track in one direction. Several molecular walkers had already been realized based on DNA nanotechnology.[40,41] To perform the same task with small molecules, the introduction of orthogonal dynamic covalent bonds was the key. Starting with oligomer **6**, the "walker" subunit is on the left side, bound to the track with one disulfide and one hydrazone bridge (Fig. 3, red). Disulfide exchange from the first arene to the third arene from the left is unfavorable as long as the double bond between the second and the third arene is in *trans* configuration. Light-induced isomerization from *trans* to *cis* enables directional disulfide exchange under basic conditions from arene one in **7** to arene three in **8**. According to the analysis by nuclear magnetic resonance (NMR) spectroscopy, this process occurs with an efficiency of greater than 60%. Light-induced isomerization back from *cis* to *trans* adds strain to the central macrocycle of **9**. This strain can be released by hydrazone exchange under acidic conditions. In this directional process, the walker moves from arene two in **9** to arene four in **10**. The yield of this translocation is still above 50%. Control experiments confirm that the correct sequence of operations is needed for directional molecular motion. The walker can

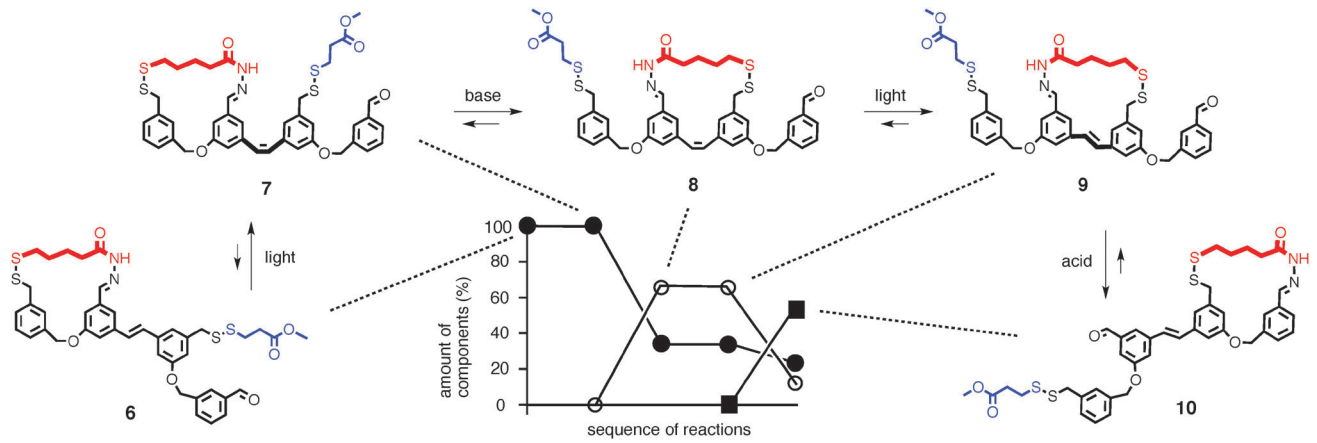


Fig. 3 Directional molecular motion achieved with orthogonal dynamic disulfide and hydrazone bridges and photoinduced olefin *cis–trans* isomerization.

be made to walk in the opposite direction simply by reversing the sequence of stimuli. The perspective to see the same process taking place on a longer polymer is fascinating.

Directional walking down the molecular track in **6** is the highlight of a series of studies on molecular motion from the group of David Leigh. Earlier reports focused on the orthogonality of disulfide and hydrazone exchange[42] and random walking without directionality.[43,44] In a complementary system, random walking was explored by the spontaneous intramolecular migration of α-methylene-4-nitrostyrene along oligoamine tracks.[45,46] This system operates with an elegant reversible intramolecular Michael–retro-Michael addition mechanism. The presence of orthogonal dynamic covalent bonds would presumably be useful to achieve directional walking in this system, although attraction of the walker fragment toward a thermodynamic sink has been demonstrated.

3.2 "Living" organic materials, multicomponent photosystems

With regard to functional materials, expectations from dynamic covalent bonds are high because their "living" nature makes them ideally suited for easily introducing structural complexity and, at the same time, promises access to challenging topics such as self-repair, self-healing, adaptive self-sorting, replication and transcription. Self-healing is very nicely documented in a recent system with orthogonal dynamic covalent bonds.[47] Disulfide-containing bishydrazones and trialdehydes were used to generate polymer network **11** where two dynamic bonds are present, *i.e.*, disulfide and hydrazone bridges (Fig. 4a). The resulting dynamic hydrogels undergo hydrazone and/or disulfide exchange to repair damages, in acidic and basic environments respectively. The polymer retains its self-healing character even in neutral conditions (where both hydrazone and disulfide exchange are kinetically hampered) if a catalytic amount of base (aniline) is added during the preparation. Moreover, this new material displays sol–gel transition in response to pH and/or redox external stimuli.

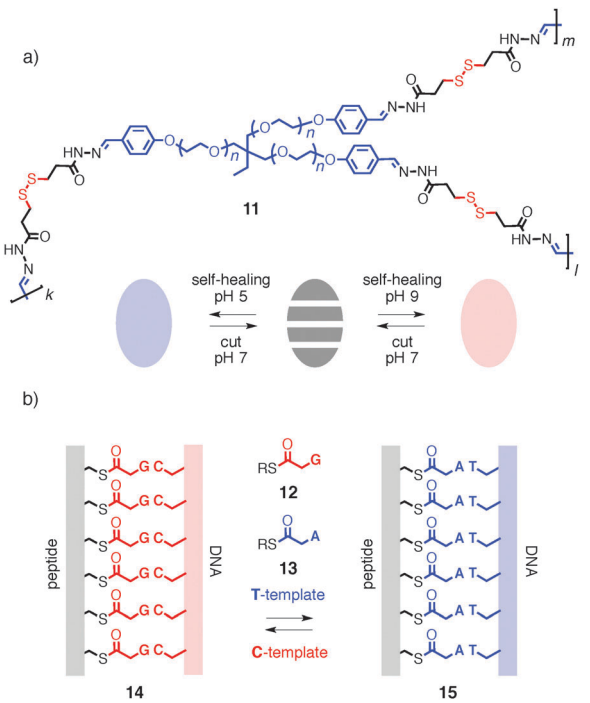


Fig. 4 (a) Supramolecular systems with orthogonal dynamic bonds that form gels that, after being cut at pH 7 (grey, striped symbol), can self-heal under basic conditions (disulfide exchange, red symbol) or acidic conditions (hydrazone exchange, blue symbol). (b) Self-repair has also been nicely demonstrated with single dynamic thioesters in sequence adaptive peptide nucleic acids (G = guanine, C = cytosine, A = adenine, T = thymine).

Sequence adaptive thioester PNAs must be mentioned at this point as examples of dynamic covalent chemistry applied to function. Although they operate with only one dynamic bond in combination with the weak interactions involved in DNA technology (Fig. 4b),[21] they nevertheless provide the perfect example to illustrate self-repair with dynamic covalent bonds at the molecular level. Thioester PNAs were constructed from peptides with a cysteine in every second position. Thioester exchange with **12** and **13** randomly attached the two nucleobases (adenine A or guanine G) along the peptide scaffold in an overall ratio of 1 : 1. Thioester exchange with **12** and **13** in the presence of a single-stranded DNA dC_{20} generated duplex **14** with a G-rich PNA (G : A ratios up to 87 : 13). Templated thioester exchange with the complementary dT_{20} gave the duplex **15** with A-rich PNAs (G : A = 11 : 89). In the transcription plot for increasing cytosine C in the DNA template against increasing A in the resulting PNA, a linear dependence was found. The key experiment for self-repair was designed as follows. An A-rich PNA was prepared by incubation with a dT_{20} template. The dT_{20} template was then replaced by a dC_{20} template, and thioester exchange with **12** and **13** was reinitiated. A spectacular inversion of the G : A ratio from 12 : 88 to 70 : 30 demonstrated the existence of self-repair in the presence of dynamic covalent thioester bonds. Similar fidelity was observed for the sequence specific formation of oligoimines along complementary DNA templates.[48]

The advantages of using dynamic covalent bonds to build surface architectures have begun to be recognized only recently.[49,50] Orthogonal dynamic covalent bonds are particularly attractive for growing functional multicomponent architectures directly on solid surfaces. For this purpose, self-organizing surface-initiated polymerization (SOSIP)[51,52] and templated stack exchange (TSE)[53] have been introduced as general synthetic methods that operate with disulfide exchange and hydrazone exchange, respectively (Fig. 5 and 6).

In SOSIP, initiator **16** and propagator **17** are required to contain a functional component in the middle (naphthalene-diimide core) able to generate π-stacks, so they can transport electrons efficiently. This core is embedded in self-organizing (lysine-derived diamides) and polymerizing components (cysteine in initiator **16** and a strained cyclic disulfide in propagator **17**). The initiator incorporates two diphosphonate "feet" that allow it to bind to an oxide surface (usually indium tin oxide, ITO), after which its thiols are deprotected and deprotonated to initiate SOSIP. Self-organization is expected to place the two strained cyclic disulfides in propagator **17**

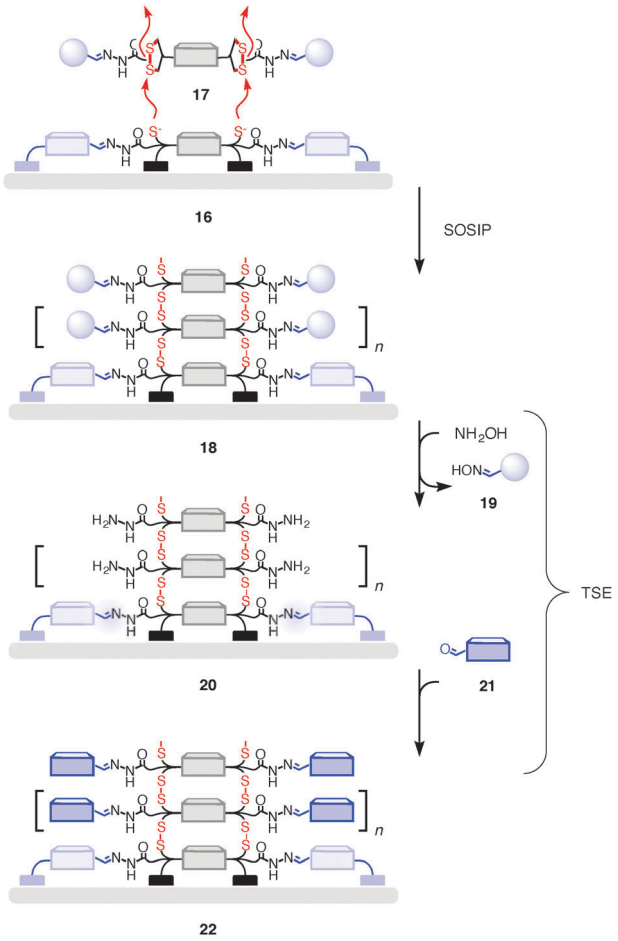


Fig. 5 General synthetic access to functional multicomponent surface architectures is secured by self-organizing surface-initiated polymerization (SOSIP) using disulfide chemistry followed by templated stack exchange (TSE) with orthogonal hydrazone chemistry.

directly on top of the initiator's thiolates. Ring-opening disulfide exchange binds the propagator to the surface and regenerates two thiolates for continuing SOSIP. The resulting ladderphane[54] surface architectures **18** – smooth, self-organized over long distances down to the molecular level without significant defects – have been characterized in many variations by many different methods.

Quite extensive screening of other existing methods suggests that the newly invented surface-initiated disulfide-exchange polymerization is an excellent means for constructing complex surface architectures in a facile and general way. Consistent with expectations from dynamic covalent chemistry, the occurrence of self-repair during SOSIP has been demonstrated.[52] The dynamic nature of the disulfide bond also accounts for intrinsic templation efficiencies up to 97% achieved for self-sorting when SOSIP is carried out with a mixture of different propagators (co-SOSIP).[55] Similar to templated polymerization in solution (*e.g.*, sequence-adaptive PNAs **14** and **15**,[21,48] or the central dogma in biology), the development of synthetic methods that operate on the transcription of information will likely be unavoidable for the creation of highly sophisticated multicomponent surface architectures.

Orthogonal dynamic covalent bonds have been the key to the introduction of TSE, another synthetic method conceived to build increasingly complex multicomponent surface architectures. For TSE, SOSIP is performed using initiator and propagator monomers bearing hydrazone-based cleavable templates that become incorporated into the π-stacks formed (blue spheres in **18**, Fig. 5). The templates along the SOSIP stack in **18** are then removed with excess hydroxylamine, releasing **19**. The holes left behind in **20** are filled with aldehydes **21** of free choice. The hydrazone exchange used for TSE is orthogonal to the disulfide exchange used for SOSIP. Dynamic covalent chemistry is thought to be as essential for TSE as for SOSIP. Multiple equilibria will be expected when drilling the deep pores in the surface architectures **20**. The obtained architectures **22** contain co-axial stacks of variable nature, a motif that is of high interest in materials science, particularly optoelectronics, including organic solar cells.

The power of SOSIP–TSE has been exemplified with many variations.[53,55–58] Highlights include double-channel photosystem **23** with antiparallel redox gradients (so-called OMARG-SHJs, supramolecular *n*/*p*-heterojunctions with oriented multicomponent antiparallel redox gradients, Fig. 6).[53] Thanks to orthogonal dynamic covalent bonds, the directional synthesis of surface architectures as complex as **23** is fairly straightforward. It begins with SOSIP using a propagator based on a colorless, unsubstituted naphthalenediimide (NDI) core. To create a redox gradient in the SOSIP stack, the ITO electrode is simply dipped into a new solution of a propagator based on a yellow, bis-ethoxy-substituted NDI core. Both NDIs transport electrons along their stacks. The NDI cores' respective LUMO energies direct the flow of electrons toward the solid surface (LUMO: lowest unoccupied molecular orbital). With TSE, a two-component stack of red NDIs is installed with an oriented antiparallel gradient that directs the flow of holes in the HOMOs (highest occupied molecular orbitals) away from the solid surface. Once light-generated excitons charge-separate in photosystem **23**, the resulting electrons and holes are transported in opposite directions in a manner reminiscent of biological photosystems. The functional importance of antiparallel gradients was confirmed by the dependence of the short-circuit photocurrent density J_{SC} on the power of irradiation. The recombination efficiency, calculated from the slope, is as low as 22% in photosystem **23**. With only one or no gradient, recombination efficiencies rise to 50–53%; with misoriented gradients, recombination becomes dominant.

Another advance in the evolution of SOSIP–TSE is the very recent construction of triple-channel architectures such as **24** (Fig. 6).[58] In this architecture, central SOSIP stacks are built with NDIs using disulfide exchange chemistry as described. A central squaraine channel is attached by TSE using hydrazone exchange. The third channel composed of fullerene stacks is attached *in situ* before TSE *via* an oxime bond. Oximes are much more stable than hydrazones or imines and often not considered as dynamic covalent bonds. Compared to the poorly active photosystem with one NDI and one squaraine channel only, the addition of the fullerene channel increased photocurrent generation more than 10 times.

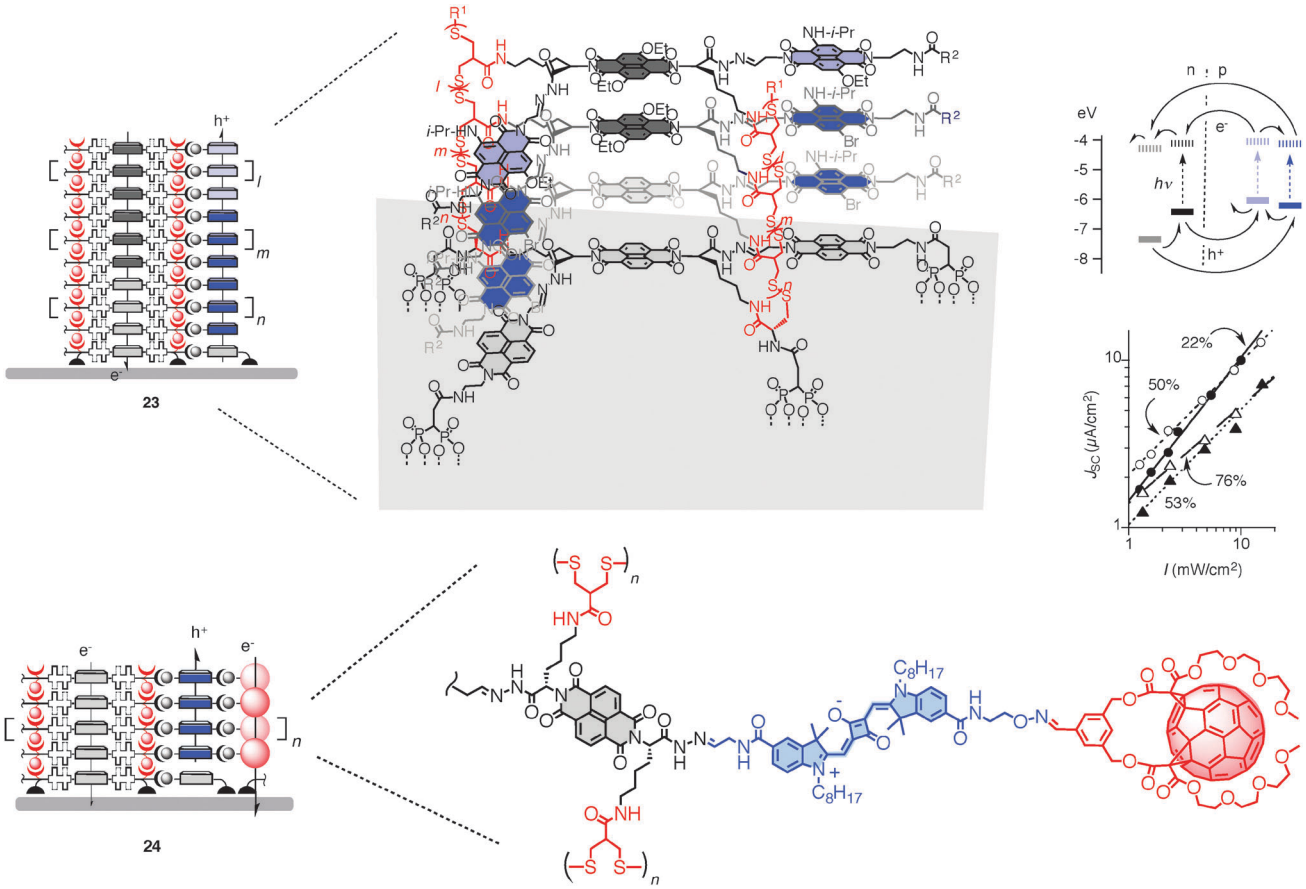


Fig. 6 Representative double-channel photosystems with antiparallel redox gradients (top) and triple-channel photosystems (bottom) obtained by SOSIP–TSE on ITO surfaces (grey). Frontier molecular orbital levels and recombination efficiencies are given for **23** (filled circles) in comparison with controls without (empty circles, filled triangles) and misoriented gradients (empty triangles). Adapted from ref. 53 with permission, © 2011 American Chemical Society.

Very recently, orthogonal dynamic covalent bonds have been employed in the construction of resin-bound dynamic combinatorial libraries.[59,60] These libraries on solid support have been introduced to simplify the analytical problems associated with solution-phase libraries. In a typical screening strategy, one half of a dimer is immobilized on a synthesis resin; its complementary half is selected from a mixture in solution. The binding of fluorescent target molecules to the solid library can then be easily used to identify biologically active inhibitors.[59] To expand this approach to libraries of three-component inhibitors, orthogonal dynamic covalent disulfide and hydrazone bridges have been tested by the Miller group in a proof-of-principle study.[60] Good conditions to form, isolate and disassemble trimers such as **25** in solution and on solid support have been determined (Fig. 7).

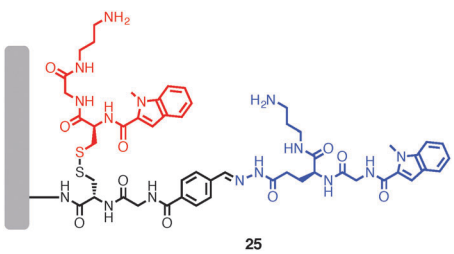


Fig. 7 A model product for a resin-bound dynamic covalent three-component library with orthogonal disulfide and hydrazone bridges.

3.3 Molecular recognition and transformation

Freely exchanging dynamic combinatorial libraries can explore large regions of chemical space, allowing them to find the global thermodynamic minimum. When this thermodynamic minimum involves a supramolecular binding event to a particular guest, the system can rearrange so that it contains the best possible host for that guest. The work of optimization is effectively done by the library, often returning surprising structures as a result.

The scope of this process may be appreciated by considering the range of substrates for which receptors have been found. The Furlan group used a two-step evolutionary process to develop the macrocyclic lithium receptor **26** (Fig. 8a).[61] A hydrazone- and disulfide-bearing monomer was allowed to equilibrate under hydrazone-exchange conditions in the presence of lithium bromide. The resulting macrocycle was then subjected to a second round of optimization in which disulfide exchange was used to modify the macrocycle's periphery. The surprising

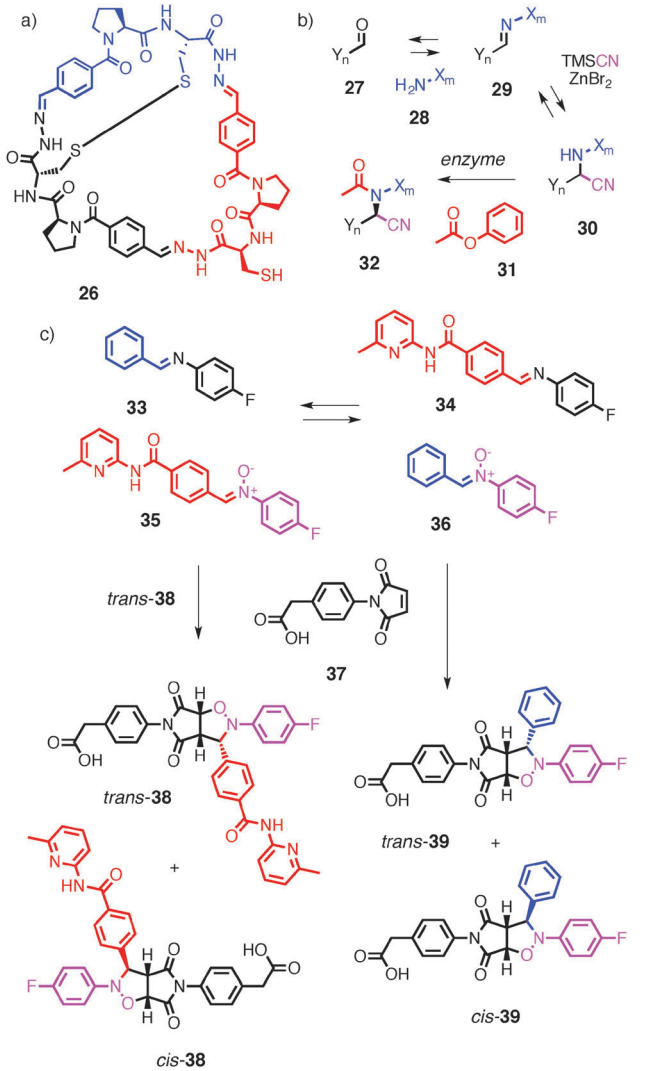


Fig. 8 Molecular recognition and transformations with formal orthogonal dynamic covalent bonds.

degree of lithium incorporation of macrocycle **26**, as determined by mass spectrometry, was attributed to rigidification of the macrocycle by the bridging disulfide bond. This bridge is thought to constrain the macrocycle into a conformation ideal for lithium binding.

Combinatorial chemistry and dynamic kinetic resolution have been elegantly employed to form carbon–carbon bonds around a stereogenic center with high enantiopurity (Fig. 8b).[62] A mixture of aldehydes **27** and amines **28** under dynamic exchange conditions resulted in a combinatorial library of imines **29**. Addition of a cyanide source, acetic acid and $ZnBr_2$ effectively coupled the reversible transimination to a reversible Strecker reaction, resulting in a combined library of imines **29** and Strecker adducts **30**, all freely exchanging at equilibrium. While the library initially generated through reversible transimination was made up exclusively of achiral imine molecules, the Strecker adducts **30** are chiral. The library formed was a racemic mixture, and as such was amenable to dynamic kinetic resolution. A chiral lipase derived from *Pseudomonas cepacia* was used to catalyze an irreversible reaction with phenyl acetate **31**, collapsing the library into just three products **32**. The library generated chemical diversity and populated the chemical space, allowing the enzyme to select from this library the members which react with lowest activation energy barriers. This is a nice example of chemical transformations with formal orthogonal dynamic covalent bonds because they are coupled in series rather than in parallel as usual.

In a system reported by Sadownik and Philp, the catalyst and substrate were identical, and a library with formally orthogonal dynamic covalent bonds was used to find the ideal autocatalyst (Fig. 8c).[63] A dynamic combinatorial library of two imines **33** and **34** and two nitrones **35** and **36** was allowed to react with maleimide **37** to form a variety of possible products **38** and **39**. Of these products, *trans*-**38** was shown to be an excellent catalyst for its own formation, accelerating the cycloaddition reaction between **35** and **37** by a factor of more than 100. Because the supply of **35** is continually being renewed through dynamic exchange, autocatalyst *trans*-**38** is able to self-replicate at the expense of other species until the cycloaddition product mixture consists almost entirely of *trans*-**38**. This minimalist dynamic, autocatalytic system is not only of interest to the development of functional materials but also has a bearing on theories of the origin of life.

Formal orthogonal dynamic covalent bonds have also been used in chemical protein synthesis where joining two or more large peptide sequences cleanly and efficiently is not a trivial task. Recently, the commonly used strategy of native chemical ligation has been expanded by incorporating a cyclic disulfide (Fig. 9).[64] Native chemical ligation is a two-step process beginning with the reversible attack of a thioester **40** by a thiol **41**; the cyclic disulfide in **41** is stable under these conditions. Once the reversible thioester exchange has been kinetically captured by a vicinal amine in **42**, the cyclic disulfide in product **43** can be orthogonally reduced to the pair of thiols in **44**.

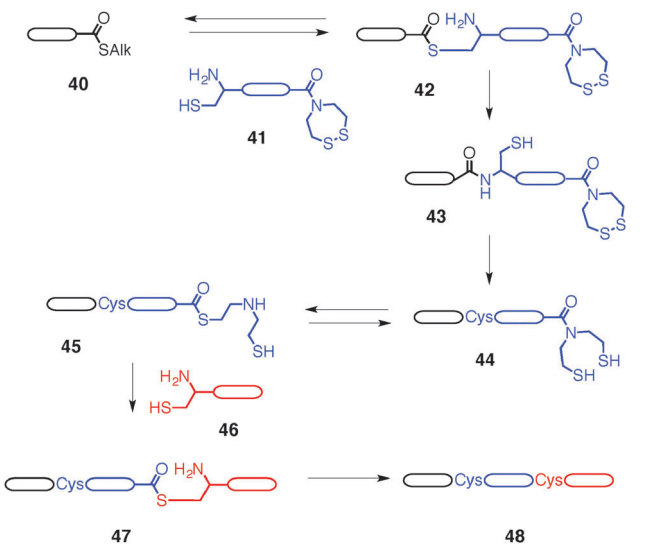


Fig. 9 Formal orthogonal dynamic covalent bonds in advanced native chemical ligation.

Intramolecular amide–thioester exchange converts **44** into **45** for a subsequent native chemical ligation with thiol-terminated peptide **46**. Intermolecular thioester exchange yields **47**, which is intramolecularly transformed into the final peptide **48**. This strategy, relying fundamentally on reversible reactions that are independently addressable, has been employed to construct large, biologically active oligopeptide sequences in a one-pot sequence of reactions. Although the dynamic nature of disulfides is not really used, it is nevertheless an interesting example, both for the promise of this kind of chemistry in synthetic transformations and also because of the loose and somewhat incomplete definition of orthogonal dynamic covalent bonds.

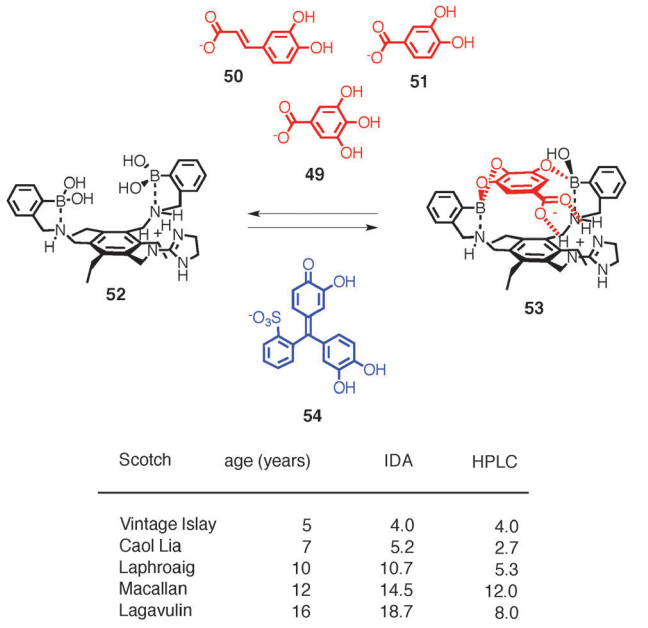
3.4 Chemo- and biosensors

The use of dynamic covalent bonds in sensing systems is quite common. A wonderful early example is a colorimetric chemosensor to determine the age of whisky (Fig. 10).[65]

The age of Scotch is best determined from the concentration of natural products extracted over the years from the oak barrels. The most abundant gallate **49** would be an obvious analyte, but high-pressure liquid chromatography (HPLC) analysis does not correspond well with the reported age of the whiskies tested. The problem is that although the total concentration of all members of the gallate family appears to remain constant, the concentrations of individual members tend to fluctuate. Other family members include coffeic acid **50** or 3,4-dihydroxybenzoic acid **51**.

The bis-boronic acid **52** was designed to sense the entire gallate family of natural products, exemplified here with **49**–**51**. Dynamic covalent bonds with the catechols contribute the most to form product **53**. π–π Interactions and ion pairing between carboxylate and guanidinium complete the binding. For colorimetric detection, the indicator displacement assay (IDA) was used. In this assay, pioneered by the Anslyn group, the receptor is loaded with a chromophore of related structure. Pyrocatechol violet **54** was selected because it reproduces the catechol motif and the negative charge of the gallate family. Binding to receptor **52** changes the color of **54**. Displacement of **54** by the gallate analyte restores the original color of the free chromophore. With the use of IDA, the determination of the age of Scotch gives correct trends and is possible with the naked eye.

A similar catechol sensing system that makes use of orthogonal dynamic covalent bonds was recently reported by the Bode group (Fig. 11).[14] In chemosensor **55**, two boronic acids have been attached to a bullvalene core. These bicycles are wonderful examples of dynamic covalent chemistry because spontaneous Cope rearrangements lead to the coexistence of a large number of configurationally distinct isomers. Analysis of these dynamic mixtures is very demanding, although the isolation of a single pure bullvalene isomer has been reported last year.[66] Previously, bullvalenes have been equipped with two porphyrins for the adaptive sensing of fullerenes.[67–69] To sense polyphenols, the ^{13}C labeled bullvalene **55** was prepared.[14] Equilibration of the 860 possible isomers produced a signature in the ^{13}C NMR spectrum that could be treated as a fingerprint of the free sensor. In the presence of epigallocatechin gallate (EGCG) **56** as a model polyphenol, this ^{13}C fingerprint changes



Scotch	age (years)	IDA	HPLC
Vintage Islay	5	4.0	4.0
Caol Lia	7	5.2	2.7
Laphroaig	10	10.7	5.3
Macallan	12	14.5	12.0
Lagavulin	16	18.7	8.0

Fig. 10 A sensor for the age of Scotch that operates with indicator displacement assay (IDA) based on dynamic covalent boronic ester exchange. Results are compared to HPLC data for gallate only. Data are normalized to 4 for the lowest value.

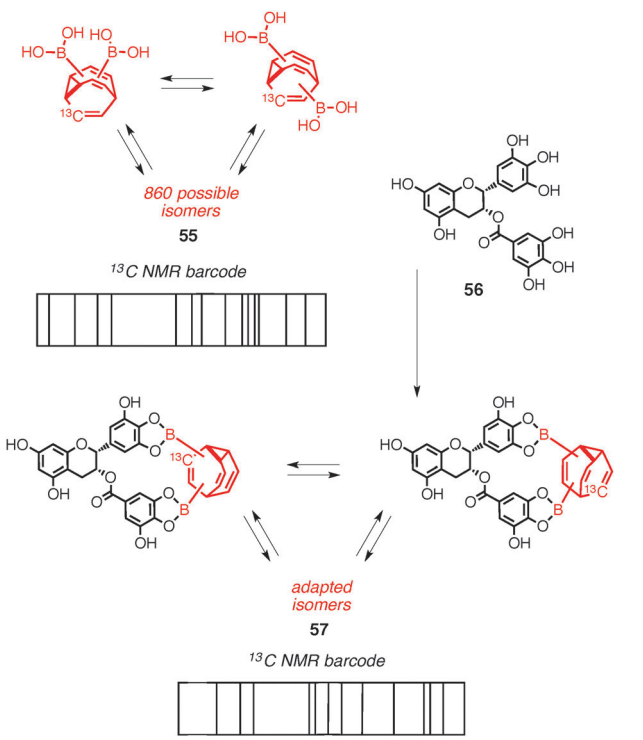
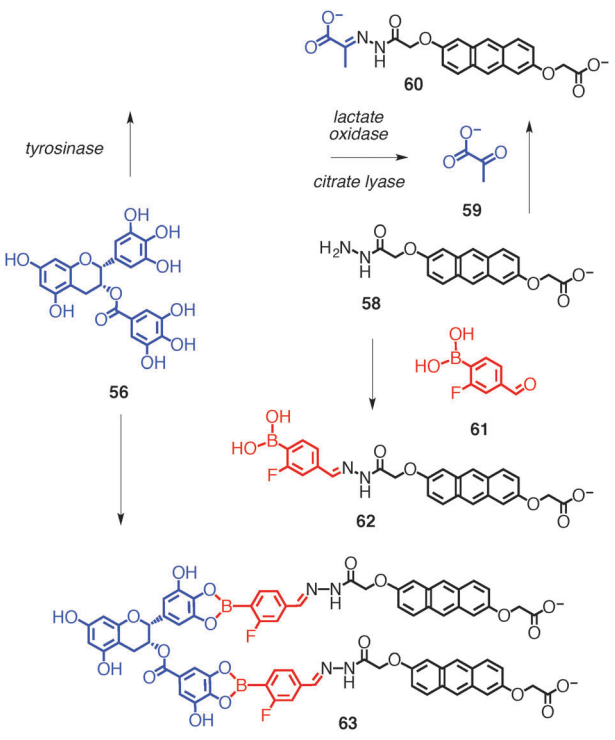


Fig. 11 A polyphenol sensor that operates with orthogonal dynamic boronic esters and shapeshifting bullvalenes. A ^{13}C label generates analyte-specific signatures in the ^{13}C NMR spectra.

because the formation of two boronic esters as in **57** changes the equilibria among the bullvalene isomers. Tests with a representative collection of polyphenols suggested that the obtained ^{13}C signatures are unique for each analyte.

Similar polyphenol sensors that operate with orthogonal dynamic covalent bonds have been reported previously.[34] They are based on synthetic multifunctional pores that work in lipid bilayer membranes. The pores used were artificial β-barrels with π-acidic clamps or tweezers at their inner surface to catch π-basic analytes passing through the pore. The formation of donor–acceptor complexes within the pore is then reported as a decrease in fluorescence activity due to the hindered efflux of self-quenched fluorophore through the pore. To sense non-aromatic analytes, signal amplifiers such as **58** were introduced (Fig. 12). These bifunctional amplifiers contain a π-basic anthracene core for pore inactivation, a negative charge for solubility, and a hydrazide to covalently capture aldehyde- and ketone-containing analytes. This dynamic covalent approach was then combined with biosensing, a term that stands for the use of enzymes for signal generation. For lactate or citrate sensing in actual samples, pyruvate **59**, the product of enzymatic signal generation, was covalently captured by hydrazide **58**.[70] Pore blockage by hydrazone **60** was then reported as a decrease in fluorescence. The introduction of dynamic covalent



sample	polyphenol expected (mg/g)	found
green tea bags	72	≥ 49
Shincha leaves		≥ 111

Fig. 12 A polyphenol sensor that operates with synthetic multifunctional pores in fluorogenic vesicles that respond to boronic ester and hydrazone exchange.

signal amplifiers was the key breakthrough needed to create a molecular "artificial tongue" that operates in lipid bilayer membranes (and uses dynamic covalent chemistry)[20] like the receptors of our own tongue.[70]

An additional, dynamic orthogonal boronic ester was needed for the sensing of polyphenols such as EGCG **56** with synthetic multifunctional pores. Reaction of signal amplifier **58** with benzaldehyde **61** generated boronic acid **62** *in situ*, which was then used to covalently capture polyphenols such as **56**. This process was monitored as pore activation because, unlike the effective blocker **62**, the resulting bis-boronic ester **63** was too large to enter the synthetic multifunctional pore. To confirm that the polyphenols were responsible for the observed pore activation, tyrosinase was used to selectively remove them and thus reactivate the pore. The sensor was then calibrated with polyphenon, a commercially available polyphenol extract, and used to show that high quality Shincha leaves contain about twice as much polyphenol than green tea bags from Geneva supermarkets. The surprisingly good sensitivity in the low micromolar range prompted the study of the formation of bis-boronic ester **63** in more detail.[71] Because of the powerful exciton coupling between the two anthracenes, circular dichroism (CD) spectroscopy could be used to selectively detect dimers. The new biosensing strategy was further expanded to include catechol-free polyphenols such as resveratrol,[72] the key polyphenol in red wine that has been evoked to account for the "French paradox".

Dynamic covalent chemistry was also crucial for the construction of differential sensors that operate in lipid bilayer membranes.[73] This was surprisingly difficult to realize considering that many chemosensors and also biological olfactory systems operate this way. Pattern generation in the nose combined with pattern recognition in the brain is the only way to discriminate more than 10 000 odorants with ~350 receptors. The difficulty faced when attempting to realize differential sensing with synthetic transport systems in lipid bilayer membranes was pattern generation. The solution to this problem was dynamic covalent chemistry. For pattern generation with muscone **64** as a representative "Geneva" odorant, cationic peptide dendrons such as **65** with one to six hydrazides were prepared (Fig. 13a). Hydrazone formation then yielded cationic amphiphiles such as **66** that were able to activate DNA as cation transporters in fluorogenic vesicles.

The differences in activity obtained with different peptide dendrons were then used to generate patterns. Routine pattern recognition in the virtual principal component space revealed overlap-free discrimination for all tested odorants, including enantiomers and *cis–trans* isomers (cucumber aldehyde). The obvious choice to probe compatibility of this "artificial nose" with samples from supermarket or hospital was perfumes. The results were excellent (Fig. 13b). Early examples for the extension of this approach to orthogonal dynamic bonds will be mentioned in the context of applications in the field of cellular uptake.[74,75]

One of the first examples of functional orthogonal dynamic bonds uses formylphenyl boronic acid as in polyphenol sensor **62** (Fig. 12).[30,31] It focuses on a simple method to assess the

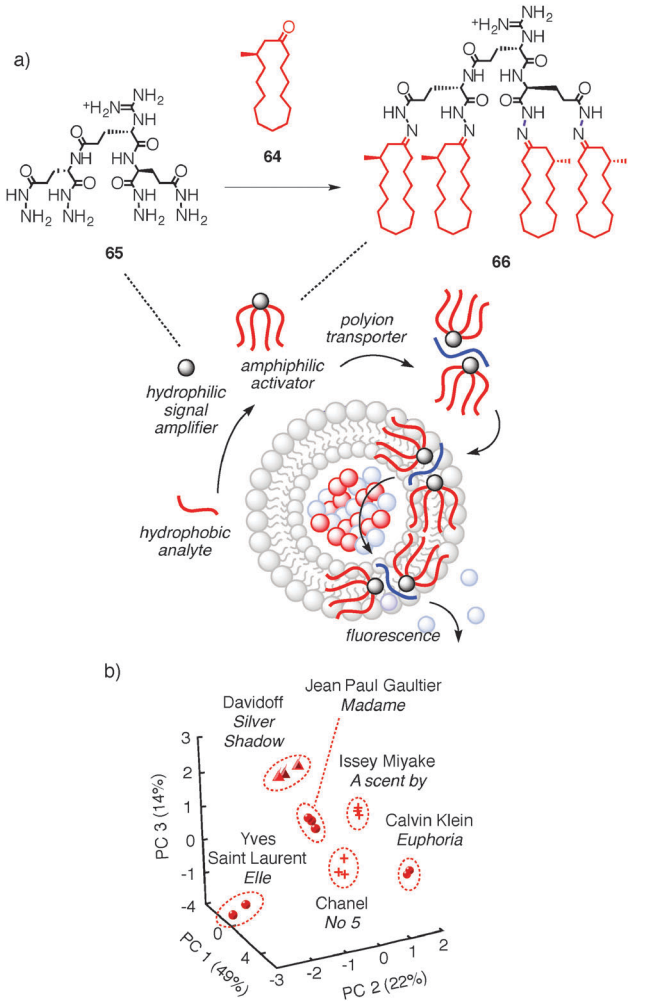


Fig. 13 An artificial nose that operates with dynamic hydrazone bridges. (a) Odorants such as muscone **64** are covalently captured by charged hydrazides such as **65**. The obtained amphiphiles **66** activate DNA as a transporter in fluorogenic vesicles. (b) Different activities obtained with different hydrazides are used to generate patterns, principal component (PC) analysis for pattern recognition of odorants or perfumes in the virtual PC space. Adapted from ref. 73 with permission, © 2011 Royal Society of Chemistry.

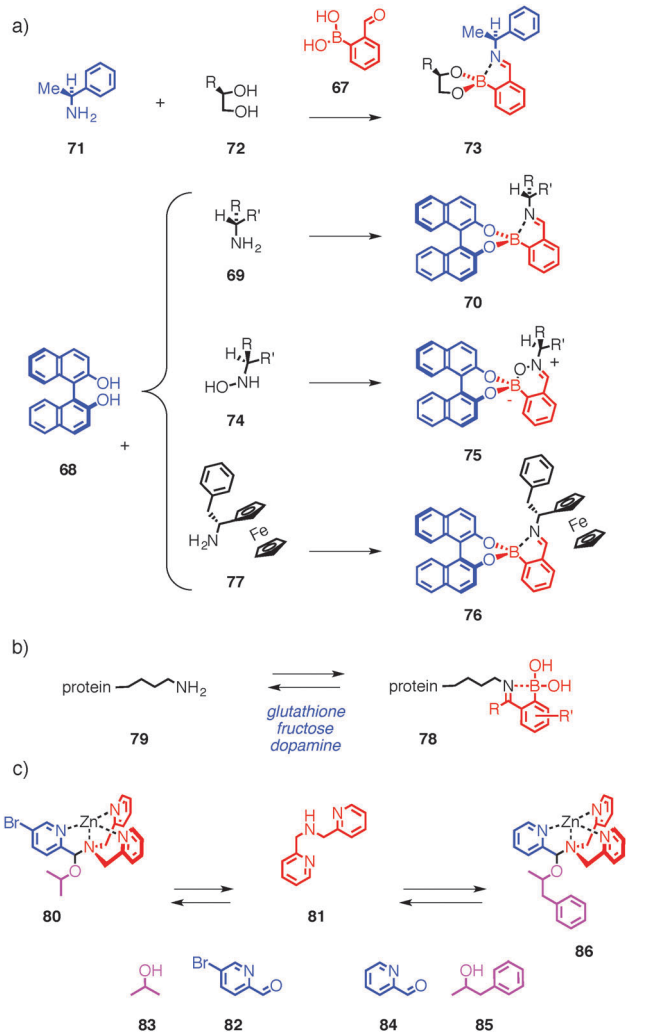


Fig. 14 Bifunctional chirality sensors that work with orthogonal dynamic covalent bonds. Twofold covalent capture by benzaldehyde **67** is used to (a) determine the enantiopurity of chiral diols **72**, amines **69** or **77**, and hydroxyamines **74** by NMR spectroscopy or cyclic voltammetry, and to (b) reversibly label accessible lysine residues of proteins. (c) Dynamic covalent multicomponent systems such as **86** sense the chirality of secondary alcohols.

enantiomeric excess of different chiral primary amines by NMR spectroscopy. The approach relies on the rapid formation of a three-component adduct between the achiral bifunctional connector **67**, (*P*)-binol **68** as an enantiopure aromatic diol, and a chiral primary amine **69** (Fig. 14a). The resulting diastereomeric iminoboronates **70** were rigid enough to generate an anisotropic effect on the amine moiety, leading to different chemical shifts in the ^{1}H NMR spectra. This approach is not limited to α chiral amines, but can also be applied to primary amines containing remote stereogenic centers.

In a complementary approach, an enantiopure primary amine, (*S*)-(α)-methylbenzylamine **71**, was reacted with 2-formylphenylboronic acid **67** and different chiral diols **72**, yielding diastereomeric iminoboronate esters **73**. The quantification of the enantiomeric purity of the tested diols (1,2-, 1,3- and 1,4-diols were tested) was achieved *via* the direct integration of the signals due to each diastereomer, with ee values up to 98% accurately reported. The same approach was successful in determining the enantiopurity of chiral hydroxylamines **74**.[76] Simple mixing with 2-formylphenylboronic acid **67** and binol **68** gave the three-component diastereomeric nitrono-boronate esters **75**. The means of detection was not limited to NMR spectroscopy. Established alternatives include CD spectroscopy and, remarkably, even cyclic voltammetry.[77] For this purpose, the chiral ferrocene derivative **76** was prepared from the enantiopure ferrocene amine **77** and 2-formylphenylboronic acid **67**. The resulting Schiff base was coupled with (*P*/*M*)-binol **68** to give diastereomeric ferrocene boronate esters **76**. These diastereomeric esters showed different behavior in square wave voltammetry and cyclic voltammetry. It was then possible to discriminate between mixtures with different degrees of enantiomeric excess of binol, simply by monitoring the potential values. The described method

was powerful enough for an accurate determination of ee in the range of 60–98%, with an estimated error lower than 3%.

The same bifunctional 2-formylphenylboronic acid **67** has recently been used to achieve reversible protein modification (Fig. 4b).[78] This compound was able to form iminoboronates **78** between free amino groups present in the protein (*N*-terminal and ε-amino group of lysine, represented in **79**). Iminoboronate formation is possible in water at room temperature with high efficiency only when the carbonyl group is placed in proximity (*ortho* position) to the boronic acid moiety, due to the stabilization of the dative nitrogen–boron bond (confirmed by computational simulations). The approach was successfully applied both to a small natural neuropeptide (somatostatin) and to model proteins (lysozyme, cytochrome c, ribonuclease A and myoglobin). Moreover, the reversibility of the approach was demonstrated: The presence of endogenous molecules such as glutathione, fructose or dopamine promotes imine hydrolysis, releasing the protein in the original unmodified form.

A recent, elegant approach to determine the enantiopurity of secondary alcohols makes innovative use of dynamic covalent chemistry (Fig. 14c).[15] The multicomponent system **80** is composed of the secondary amine **81** that is able to form an unstable imminium with aldehyde **82**, which in turn reacts with isopropanol **83**. This multicomponent system is able to incorporate secondary alcohols with high sensitivity because the hemiaminal ether is stabilized by the coordination to a zinc cation placed directly above by the three N-heterocyclic ligands. Subcomponent exchange experiments covered different pyridine ligands, including **84**, and the incorporation of chiral alcohols such as **85**, 1-phenylethanol, 3-methyl-2-butanol or 2-butanol induces a twist in the ligand. This twist then results in strong exciton coupling in the CD spectra of the resulting multicomponent systems such as **86**, thus revealing the presence and enantiopurity of the chiral secondary alcohol.

3.5 Uptake and release

The use of dynamic covalent bonds has been extensively explored in the field of cellular uptake. The general idea is to destroy the active transport system under specific (acidic or reductive) conditions, either during or after uptake, to minimize cytotoxicity and to release the substrate. Cell-penetrating poly(disulfide)s are currently regarded as the transporters of the future because they are depolymerized by glutathione in the cytosol.[18] Last year, it was reported that cell-penetrating poly(disulfide)s could be grown directly on substrates of free choice by ring-opening disulfide-exchange polymerization.[79] Given the promise of cell-penetrating poly(disulfide)s, it is surprising to note that disulfide-exchange chemistry has not yet been successfully complemented by orthogonal dynamic covalent bonds. The only reported example that really matches the topic of this review is cell-penetrating poly(disulfide) **87** (Fig. 15).[80] The polymer contains the biodegradable poly(disulfide) backbone and positive charges in the backbone and side chains to ensure transport activity in lipid bilayers. Finally, a large fraction of the lateral amines were converted into amides to install phenyl boronic acids. They were expected to form dynamic boronic esters with glycosaminoglycans (GAGs) present on the cell surface. The main consequence of the introduction of boronic acids in **87** was an increase in toxicity. However, this observed toxicity is not intrinsic for boronic acids. Marvelous examples exist of cellular uptake mediated by boronic esters at the cell surface without other orthogonal dynamic covalent bonds being involved.[81] Disulfide exchange chemistry at the cell surface is currently suspected to be responsible for mediating cellular uptake in a similar manner.[82]

The use of hydrazone bridges in cationic amphiphiles has already been mentioned in the context of differential sensing (see above).[73–75] Dynamic imine amphiphiles such as **88** and **89** have also been explored in the context of stimuli-responsive micelles and vesicles.[83,84] For cellular uptake, amphiphiles with acid-labile hydrazone bridges including the doubly charged

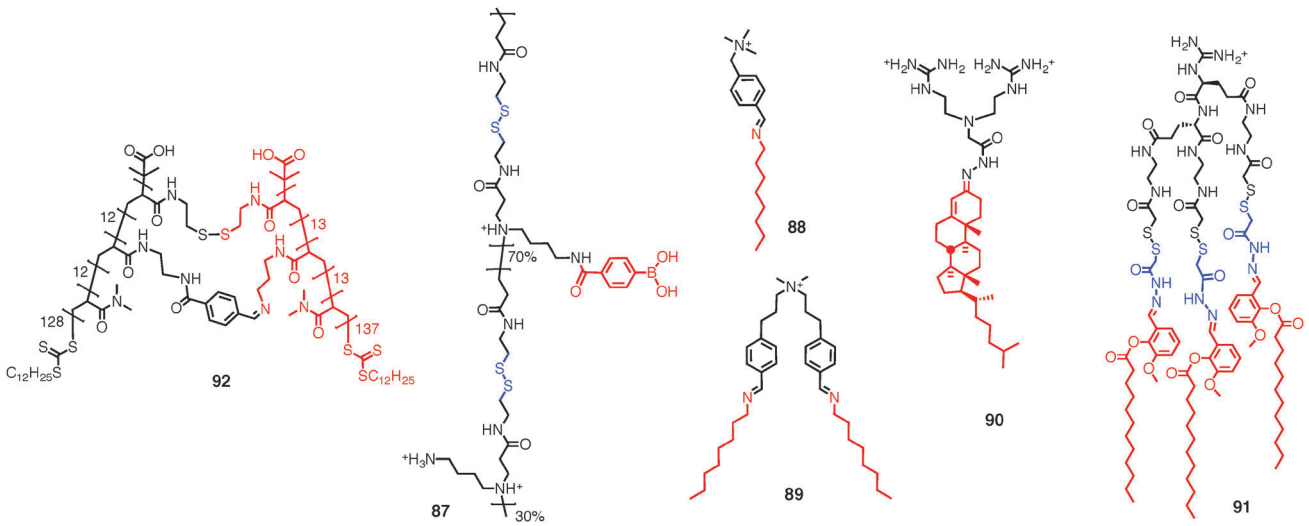


Fig. 15 Functional architectures with orthogonal dynamic covalent bonds for cellular uptake (**87**, **91**) and release (**92**), together with cationic amphiphiles with only one dynamic bond (**88–90**).

steroid conjugate **90** have been explored to deliver genes and drugs.[85,86] Their dynamic nature has provided facile access to large amphiphile libraries.[75] GFP-knockdown assays have been developed for the automated screening of these libraries for small interfering RNA (siRNA) uptake into HeLa cells (GFP: green fluorescent protein). The best hits found were almost twice as active as the best commercially available control (lipofectamine). The few examples with orthogonal disulfide and hydrazone bridges were moderately active. Amphiphile **91** with one positive charge, three tails and an additional biodegradable ester bond was among the best.[75]

The usefulness of dynamic covalent bonds to achieve stimuli-responsive substrate release is not limited to cellular uptake. One of the most spectacular applications of hydrazones focuses on the slow release of aldehyde- and ketone-containing odorants.[87] Chemoorthogonal release with dynamic imine and disulfide bridges in nanoparticles generated by **92** has been reported recently.[88] Here, orthogonal reversible reactions were used in tandem to allow precise control of the release of an encapsulated dye molecule. The nanoparticles consist of two polymers that contain disulfides and aldehydes or amines that are blended together in the presence of the hydrophobic dye Nile Red. Crosslinking between the two polymers may be achieved either by disulfide exchange in the presence of the reducing agent dithiothreitol (DTT) or by imine formation at pH < 5.5. These orthogonal processes may be carried out independently of each other, creating nanoparticles that are held together either by only imine bonds, by only disulfide bridges, or by both. In order to release the encapsulated dye molecules, all that is required is to cleave the crosslinks and destroy the nanoparticles. The orthogonality of the crosslink-forming reactions is mirrored exactly by the conditions required to cleave them. It was found that the imine-crosslinked particles could be disassembled to release the encapsulated dye by treatment with acid, and disulfide-crosslinked particles could be disassembled by treatment with a reducing agent. The nanoparticles formed by **92**, containing both disulfide and imine bonds, would disassemble only in the presence of both a reducing agent and a pH < 5.5. The system **92** is therefore a chemical AND gate, releasing its cargo when the two decoupling stimuli are applied simultaneously but remaining intact when either stimulus is applied in isolation.

4 Epilogue

In the field of supramolecular chemistry, dynamic covalent chemistry has attracted more and more interest in recent years. This is due to the fact that it combines the robustness of "classical" covalent bonds with the flexibility typical for non-covalent interactions, permitting the development of complex nanostructures. Despite the large number of functional systems in the literature that operate with one type of dynamic covalent bond, functional systems based on more than one type of dynamic covalent bond are rare. This is surprising considering that non-covalent bonds are used best together to achieve function. With this review we have tried to underline the possibility for chemists to generate complex functional systems with orthogonal dynamic covalent bonds. A remarkably broad variety of activities have been covered in a short time. However, what really stands out is that most studies ask unusual, complex and highly original questions that are hard to address with other approaches. Emphasis is on molecular systems that can not only sense, transport and transform like ordinary functional systems often do but also self-sort, self-heal, adapt, template, amplify, exchange, replicate, transcribe, or even walk and "think" (logic gates).

These pioneering off-road adventures nicely outline perspectives for the future. Namely, the impact of orthogonal dynamic covalent bonds will not be limited to a specific topic but will concern diverse topics without direct relation except that they all address unusual questions that are otherwise difficult to address. With the perspective to couple self-healing with self-sorting and logic gates, applications towards the materials sciences appear most obvious and most exciting. The results available today further imply, perhaps more surprisingly, much potential for sensing applications. The general promise is to couple signal generation with signal transduction and detection. Similar cascade processes are presumably going to benefit most from orthogonal dynamic covalent bonds in catalysis. Applications of orthogonal dynamic covalent bonds toward the life sciences, finally, will focus on the coupled activation and inactivation of chemical interferants, probably identified by *in situ* selection. Sometimes, orthogonal dynamic covalent bonds appear a bit like molecular versions of the brave little tailor, catching two flies in one blow.[89] Although "seven with one blow" seems quite far away and maybe not really needed, the extension from bifunctionality toward multifunctionality with multiple dynamic covalent bonds at work together is certainly one of the most appealing perspectives for the future. The brave little tailor, after all, ended up as a king.

Acknowledgements

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