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Dynamic Approaches towards Catalyst Discovery

Giulio Gasparini,[a] Marta Dal Molin,[a] and Leonard J. Prins*[a]

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Catalyst development is a challenging task, caused by the subtle effects that determine whether a catalyst is efficient or not. Success is enhanced by using methodology that relies to a smaller extent on rational design. Combinatorial high-throughput approaches allow for a systematic exploration of chemical space, but require an easy synthetic access to structurally diverse catalysts. The use of dynamic or reversible chemistry for the construction of catalysts is an attractive option as it allows for self-assembly and self-selection processes. Synthesis is restricted to the building blocks after which diversity is simply generated upon mixing. Self-selection of the best catalyst by the target reaction relieves the burden of rational design. Molecular systems exhibiting catalysis as an emerging property due to a cooperative interplay of the molecular components are envisioned for the future.

1. Introduction

Catalyst discovery is one of the central themes of chemistry because of the growing need for highly efficient and selective chemical transformations with a low environmental impact.[1] Catalyst discovery is very challenging as it requires the identification of species able to stabilize elusive and transient transition states along the reaction pathway. Combinatorial approaches have been introduced that permit the high-throughput synthesis and screening of catalysts.[2,3] Here, the difficulty lies in the accessibility of structurally diverse libraries of ligands. In that respect, catalytic systems composed of small, easily modifiable subunits are advantageous. The use of dynamic chemistry, i.e. chemistry relying on reversible bond formation (either covalent,[4] noncovalent[5] or a combination[6]), to connect these subunits offers a series of unique advantages and possibilities that will be discussed here.

In this review we describe our own contributions in this area embedded within the context of other dynamic approaches towards catalyst discovery. Three classes of catalysts will be discussed, distinguished in name by their characteristic property (Figure 1). Self-assembled catalysts are formed through noncovalent interactions between the molecular subunits. Self-selected catalysts, which have been the main focus of our studies, are identified upon the spontaneous response of a dynamic combinatorial library against a transition state analogue for the reaction of interest. Finally, a new class of self-evolving catalysts is defined to describe complex dynamic networks of molecules with catalytic properties. It should be emphasized that this is by no means an exhaustive review and only selected examples are provided that serve to illustrate key concepts.

[a] Department of Chemical Sciences, University of Padova
Via Marzolo 1, 35131 Padova, Italy
Fax: +39-049-8275239
E-mail: leonard.prins@unipd.it

Giulio Gasparini (left) was born in 1981 and studied Chemistry at the University of Padua, where he obtained his degree in 2005. In 2008, he received his PhD degree working on catalyst discovery using dynamic covalent capture, under the supervision of Prof. Paolo Scrimin and Dr. Leonard Prins. He is currently covering a postdoctoral position in the group of Prof. Giulia Licini, studying triphenolamine adducts as chiral catalysts for sulfoxidation reactions.

Marta Dal Molin obtained her degree in Chemistry at the University of Padova in 2008. The same year she joined Prof. Scrimin's group starting her PhD project under the supervision of Dr. Leonard Prins. The area of her research is the study of molecular recognition processes using a dynamic combinatorial approach.

Leonard Prins (right) obtained his PhD degree in 2001 from the University of Twente, Netherlands, under the supervision of David Reinhoudt. After postdoctoral periods with Peter Dervan (Caltech) and Giulia Licini (Padova), he is currently an assistant professor at the University of Padova, Italy. He has been awarded the H. J. Backerprize 2001 (Royal Dutch Chemical Society) and the "Ciamician" medal 2009 (Italian Chemical Society) and is a recipient of an ERC starting grant 2009. His research interests are the application of dynamic chemistry for receptor and catalyst discovery and the development of multivalent enzyme-like catalysts.

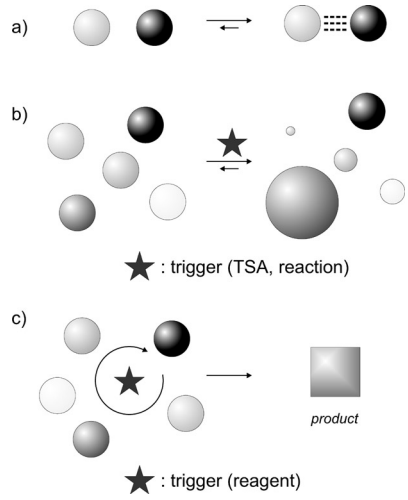

Figure 1. Schematic representations of (a) self-assembled, (b) self-selected, and (c) self-evolving catalysts.

2. Self-Assembled Catalysts

Enzymes have been, and continue to be, a fascinating inspiration for chemists interested in the development of catalysts. The superb interplay of functional groups in the active site of enzymes with the substrate *and* the transition state has led chemists to propose, often ingenious, artificial systems able to mimic (at least part of) these recognition events.[7,8] Such supramolecular systems have served as model systems to explain phenomena observed in enzymes and have permitted very detailed studies that have contributed to a mechanistic understanding of the reaction pathways involved. Although occasionally also catalytic efficiencies have been obtained that come close to the values of the natural counterparts, as a general rule the artificial systems do not live up to the expectations and industrial applications are rare.[9]

An alternative starting point for self-assembled catalysts are transition-metal-based catalysts, which are of fundamental industrial importance.[10] Here, the scope is to alter or fine-tune the properties of known organometallic catalysts via the creation of supramolecular constructs.[11] The intrinsic advantage compared to de novo enzyme development is evident: one starts with an catalytic core unit which ensures a basic reactivity or selectivity. Already more than three decades ago Whitesides et al.[12] reported in a seminal contribution on the conversion of the protein avidin into an asymmetric hydrogenation catalyst through complex formation with a biotin ligand functionalized with an achiral (diphosphane)rhodium(I) complex. The idea behind this approach was that the protein would provide a chiral environment for the achiral catalyst. Indeed, the supramolecular construct gave enantioselectivities up to around 40% for the reduction of α-acetamidoacrylic acid with no apparent loss of catalytic activity. Much more recently, this system was re-visited and optimized by Ward et al.[13] using streptavidin rather than avidin and by modulating the spacer connecting biotin to the rhodium complex. Additionally, it was shown that the catalytic performance of the construct could be improved (reaching enantioselectivities up to 96%) by altering the protein structure via site-directed mutagenesis.

A limitation of the use of proteins is that alteration of the protein structure is time-consuming and, more importantly, that only one enantiomer is available. The modulation of transition metal complexes by means of noncovalent interactions with small synthetic molecules is much more flexible and also easy amendable to combinatorial screening. The potential of this approach is nicely illustrated by the following supramolecular approaches towards the construction of diphenylphosphane ligands (Figure 2).

The initial discoveries by the groups of Kagan[14] and Knowles[15] that the use of chiral diphosphanes led to considerably higher enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of olefins compared to monodentate phosphanes caused a longstanding domination of bidentate ligands in this field. This general belief was overthrown less than a decade ago by independent observations by the groups of Reetz,[16] Pringle,[17] and Feringa[18] that chiral monodentate phosphonites and phosphoramidites gave excellent levels of enantioselectivity. This aroused great interest, which was further enhanced by the observation that mixtures of monodentate ligands behaved better than the pure ligands by themselves.[19,20] It should be noted that the mixed ligand approach had already been applied in other catalyst systems,[21] for instance mixtures of achiral salen-Mn^{III} complexes and chiral amines for asymmetric epoxidation,[22] conformationally flexible bis(phosphanyl)-biphenyl ligands with resolved 1,2-diamino-1,2-diphenylethane bound to ruthenium for enantioselective hydrogenation,[23] and achiral bis(sulfonamides) and chiral titanium alkoxide complexes for the asymmetric addition of alkyl groups to aldehydes.[24] Together with a much easier synthetic accessibility of monodentate compared to bidentate ligands, this stimulated and permitted combinatorial

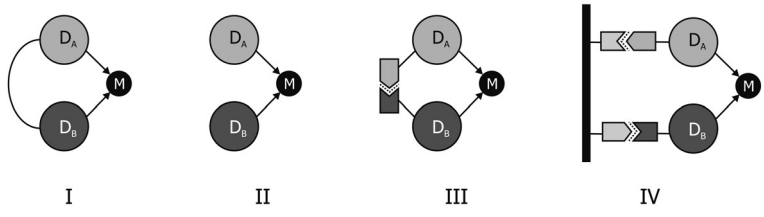

Figure 2. Heteromeric covalent bidentate ligands (I), monodentate ligands (II), noncovalent bidentate ligands (III) and templated bidentate ligands (IV).

searches for optimal ligand combinations.[25] In this context, a key contribution by the group of Breit[26] illustrated how the introduction of supramolecular recognition elements in the monodentate ligands can serve to assemble the catalyst and direct a mixed ligand system to the exclusive formation of the heteromeric complex. In a first example, the addition of rhodium to the 2-pyridone/2-hydroxypyridine tautomer system **1a/1b** equipped with diphenylphosphane ligands shifted the equilibrium fully towards the nonsymmetrical dimer **1a·1b**, which is the equivalent of a tradition covalent bidentate ligand (Figure 3, a). It was shown that the Rh complex catalyzed the hydroformylation of terminal alkenes with regioselectivities and reactivities comparable to the best covalent systems. Clearly, being based on a tautomeric equilibration this initial system did not provide access to the controlled formation of heterodimers. This was achieved using ligand sets based on aminopyridine **2** and isoquinolone **3**, mimicking the hydrogen-bonding pattern of the A-T base pair (Figure 3, b).[27] This system allowed for the first time a combinatorial screen of a 4×4 self-assembled ligand library (variations in D_x and D_y). The advantages are clear: structural variation is readily introduced in the monomeric components and structural diversity is generated simply by mixing the monodentate ligands in different combinations.

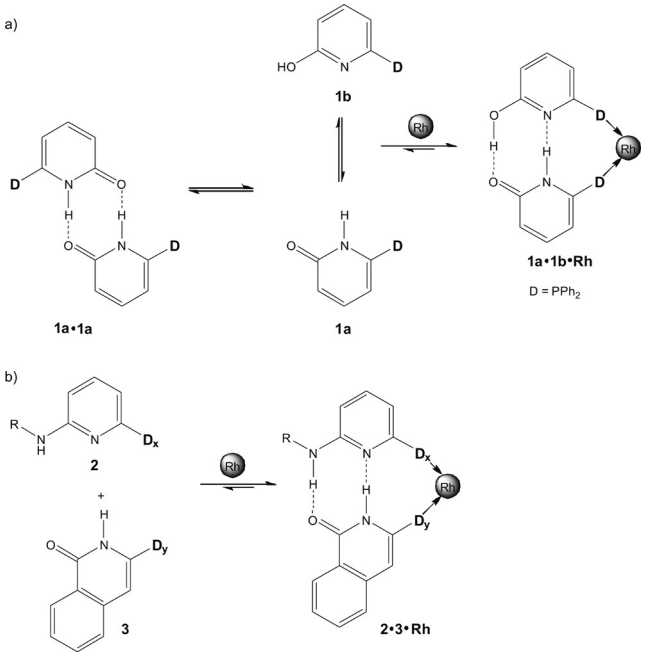

Figure 3. Self-assembled Rh-catalysts based on (a) the 2-pyridone/2-hydroxypyridine tautomer system **1a/1b** and (b) the aminopyridine–isoquinolone complex **2·3**.

At the same time, a conceptually different approach towards self-assembled catalysts was exploited by Reek, van Leeuwen and co-workers relying on the positioning of two monodentate ligands on a template driven by coordination bonds.[28] In initial studies a bis-Zn^{II}-porphyrin template was used to which pyridine phosphorus compounds were coordinated, after which the active catalyst was formed upon the addition of rhodium. Also this system displayed a catalytic behaviour in the rhodium-catalyzed hydroformylation of 1-octene comparable to covalent analogs. These studies have been successfully followed up by other groups[29–31] and the different design strategies and applications have been reviewed elsewhere.[32,33]

The self-assembly approach is by no means limited to organometallic catalysts. Clarke and Fuentes reported a library of organocatalysts for the asymmetric nitro-Michael reaction based on the H-bond driven recognition between chiral proline-based precatalysts and achiral additives.[34] Interestingly, all the catalyst combinations were more reactive than the proline catalyst by itself and also a general enhancement of diastereoselectivity and enantioselectivity was observed. A similar approach based on electrostatic interactions was reported by Mandal and Zhao.[35] Very recently, Ooi and co-workers reported on the self-assembly of the catalytically active species **4**, which is a chiral complex assembly of an aminophosphonium ion, two phenols and a phenoxide anion held together by an array of hydrogen-bonds (Figure 4).[36] Studies of the catalytic activity in the enantioselective conjugate addition of acyl anions to α,β-unsaturated acylbenzotriazole revealed that all components were required for catalytic activity.

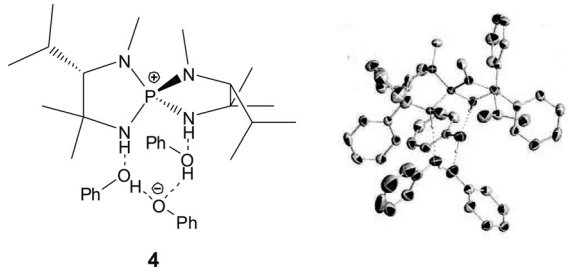

Figure 4. Self-assembled organocatalyst **4**. The X-ray crystal structure is reprinted with permission from ref 36.

From these studies a clear picture is emerging: self-assembled catalysts offer the advantage of an easy access to structural variation and combinatorial screening. The single components are either not catalytically active of perform worse than the assembly. An additional step forward is the insertion of functional groups that interact with the substrate and position it in such a manner to alter the regioselectivity of the reaction. For example, Crabtree, Brudvig et al. demonstrated the importance of substrate recognition by modifying a di-μ-oxo dimanganese catalyst with a carboxylic acid moiety.[37] Dimerization with the carboxylic acid moiety of ibuprofen enhanced the regioselectivity of the oxidation 10-fold. One can anticipate that next generation catalysts will be composed of modular units that not only self-assemble to form the active species, but will also be equipped with functional units to interact specifically with substrates. A fine example of such a multifunctional assembly was recently provided by Breit and co-workers.[38] The catalytic species is an ensemble of a monodentate phosphane ligand, a rhodium metal ion and the substrate molecule (Figure 5). The noncovalent interaction between the

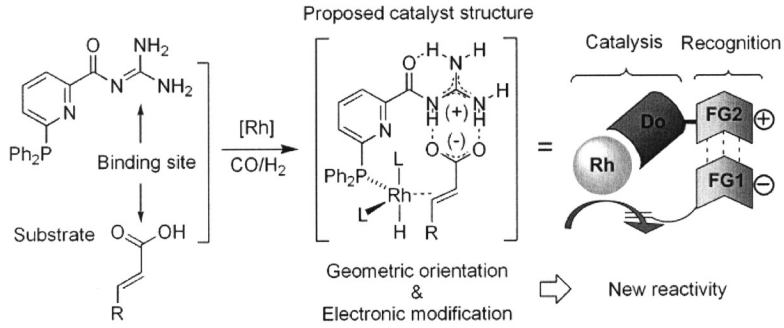

Figure 5. A recent example of a "smart" catalytic mixture relying on noncovalent interactions between catalyst, substrate and directing groups. Reprinted with permission from ref.[38]

carboxylic acid of the substrate and a guanidinium unit on the phosphane ligand combined with the coordination of the double bond to the Rh center geometrically positions the substrate for reaction and, in addition, modifies also the electronic properties. This system showed excellent catalytic activity in the hydroformylation of β,γ-unsaturated carboxylic acids with a predictable regiocontrol and substrate selectivity.

3. Self-Selected Catalysts

The successful development of the self-assembled catalysts discussed in the previous section has been strongly aided by the presence of highly functional covalent analogues, which could serve as design models. From this perspective, the development of catalysts without an a priori knowledge of their structural requisites is highly challenging. In such a case, three issues are of crucial importance for catalyst discovery. Firstly, a combinatorial library of potential (organo)catalysts has to cover a large part of chemical space. In other words, the members should have a large structural and functional variety. Secondly, ideally the chemical reaction of interest itself should identify the best-suited catalyst. Alternatively, in case screening on the reaction itself is not feasible, the transition-state of the reaction needs to be used as the target. Similar to the strategy used for the development of catalytic antibodies, catalysts can be identified based on their ability to stabilize the transition state of a reaction.[39] Thirdly, given the fact that subtle changes in a catalyst can dramatically affect its efficiency or selectivity,[15] the screening methodology should be highly sensitive to small changes in energy. In this section we illustrate, largely based on our own results, the potential of dynamic chemistry in such a project. Critical issues and potential limitations will also be discussed. Conceptually, the approach discussed in this section bears similarities to catalyst development by the immune system (catalytic antibodies)[40,41] and by the molecular imprinting of polymers.[42,43] Nonetheless, these approaches lack the element of using reversible chemical bond for catalyst formation and are therefore not included in this Microreview article.

3.1. Dynamic Combinatorial Chemistry

Dynamic combinatorial chemistry (DCC) has emerged as an attractive approach for the rapid formation of combinatorial libraries of potential receptors, materials, and also catalysts.[44–46] In a dynamic combinatorial library (DCL) the members are formed through reversible bond formation between the constituent molecules.[47] Potentially, libraries of this type cover a large chemical space, determined by the structural information embedded in the constituent molecules in terms of chemical function and ability to form reversible bonds. The reversibility of the connecting bonds, which can be either covalent or noncovalent, implies that exchange between the library members is possible. Consequently, the composition of the DCL is determined by the overall thermodynamic energetic minimum of the library. The attractive feature lies in the fact that this minimum changes upon exposure of the DCL to an external stimulus, for example the addition of a target. The target interacts with the library members and changes the thermodynamic landscape of the library. Being dynamic, the DCL will adapt and alter its composition, ideally increasing the concentration of the library member that interacts most strongly with the target. It is said ideally, because studies have illustrated that under certain conditions not the best library member is amplified.[48–50] Nonetheless, numerous examples have now illustrated that dynamic combinatorial screening can yield highly effective (and surprising) receptors.[51,52] Other applications include the development of enzyme inhibitors,[53] adaptive materials,[54] and sensors.[55] The application of DCC for catalyst development has so far been rather limited.

As a first example, Sanders, Otto and co-workers described the isolation of a catalyst for the Diels–Alder reaction between acridizinium bromide and cyclopentadiene (Figure 6, a).[56] A DCL composed of a series of macrocycles was obtained by mixing three dithiol building blocks. Considering that the transition state of a Diels–Alder reaction is very similar to the product, the product itself was used as a transition state analogue (TSA) and added as a template to the DCL. A significant shift in library composition was observed in favour of two macrocycles **5** and **6** (Figure 6, b). After isolation, it was indeed found that both

macrocycles had a high affinity for the transition state. However, a comparison with the binding affinities for the substrate showed that only macrocycle **5** bound the product stronger than the starting material, indicating that only **5** would exhibit catalytic activity. Measurements of the rates of the Diels–Alder reaction in the presence and absence of **5** and **6** indeed revealed an accelerating effect ($\approx 10\times$) for macrocycle **5** and no effect for **6**. Although rather modest in terms of efficiency, this study is of importance as it showed for the first time the self-selection of a catalyst from a DCL. In a follow-up study the same group applied the same principle for selecting a catalyst for an acetal hydrolysis reaction.[57]

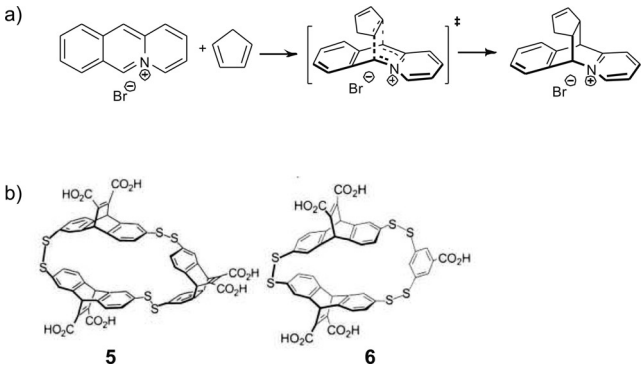

Figure 6. (a) Diels–Alder reaction between acridizinium bromide and cyclopentadiene and (b) self-selected macrocycles **5** and **6**.

The challenging aspect of catalyst discovery is that it ideally should involve a screening on two parameters: selectivity and activity, which, in enzymology terms, are defined by the Michaelis–Menten parameters K_M and k_{cat}, respectively. Accordingly, the catalyst should both recognise the substrate and the transition state.[58] It is not surprising that in enzymes the substrate and transition state recognition loci are quite often different because of the different tasks they have to accomplish.[59] A dynamic catalyst screen for both parameters simultaneously is complicated, since the concurrent addition of both a substrate and a TSA as templates to a DCL would render interpretation of the library shifts difficult. Recently, we have started a catalyst discovery program based on DCC that allows us, in principle, to screen independently on both parameters. In the following part we will discuss the concept and the results obtained so far. Our main efforts have been aimed at providing a proof-of-concept and at developing analytical tools that facilitate the determination of the composition of dynamic mixtures.

Our approach is inspired by enzymes that display covalent catalysis, implying that the enzyme is transiently modified by formation of a covalent bond with the substrate giving a reactive intermediate.[58] It is interesting to notice that Houk et al. recently pointed out that the most efficient enzymes almost all employ a covalent catalysis mechanism. This mechanism is highly advantageous from an entropic point of view, since noncovalent interactions become intra- rather than intermolecular. In addition, the formation of the covalent bond between substrate and enzyme precisely localises the substrate in a well-defined position with respect to the catalyst, which makes this mechanism highly interesting from a design point of view. The mechanism used by chymotrypsin to cleave an amide bond is given as textbook example in Figure 7.[58] Initially, the acyl-part of the amide is transferred to the nucleophile Ser_{195}, activated by the diad Asp_{102}–His_{57}, leading to the covalent acylenzyme intermediate. Subsequently, the enzyme is re-activated via the hydrolytic cleavage of the acylated serine-unit involving hydrogen-bond mediated transition state stabilization.

As a starting point for our enquiries we focused on the second part of this mechanism. In particular, we were interested in developing a system in which the target (a TSA) would self-select functional neighbouring groups able to as-

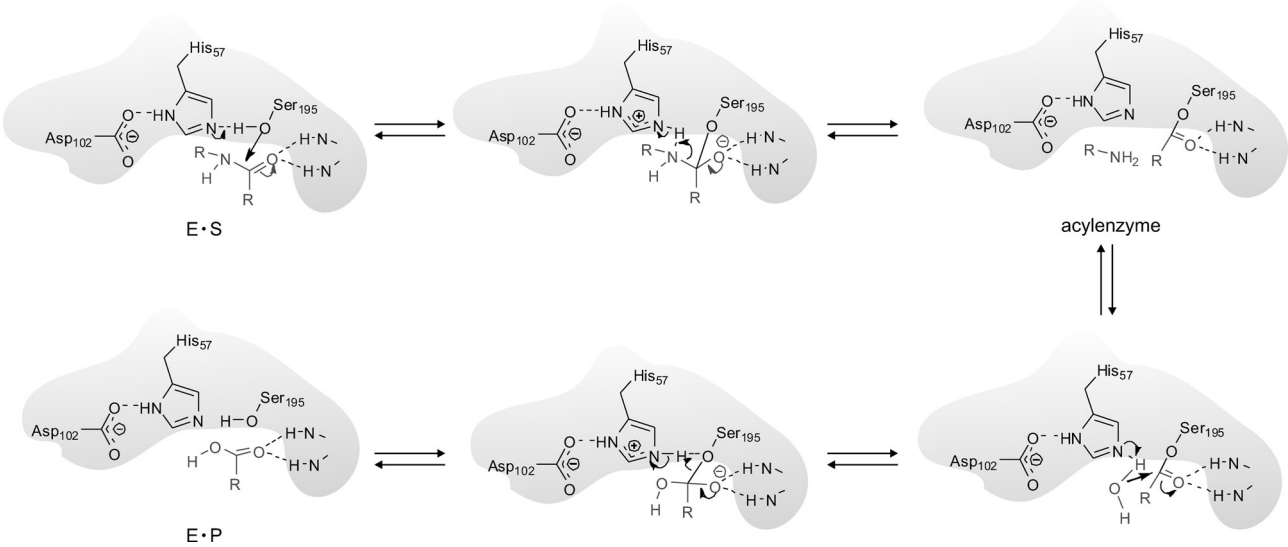

Figure 7. Reaction mechanism of chymotrypsin.

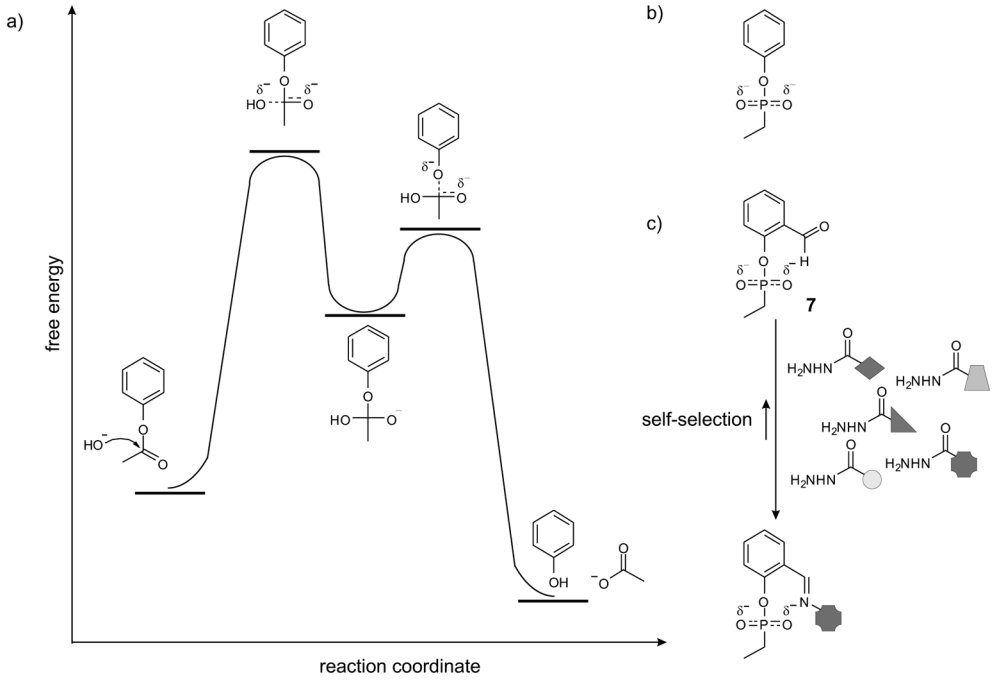

Figure 8. (a) Reaction mechanism for the basic hydrolysis of phenylacetate, (b) transition state analogue and (c) the self-selection of groups that can assist in intramolecular catalysis through transition state stabilization.

sist in catalysis. As a simple chemical model we considered the basic hydrolysis of phenylacetate, which occurs through the formation of a tetrahedral intermediate (Figure 8, a). The phosphonate group is a well-established analogue for the first transition state (Figure 8, b).[60] So, exposure of 2-[(ethylphosphinato)oxy]benzaldehyde (**7**) to a library of hydrazides should result in the self-selection of flanking functional groups able to develop stabilizing interactions with the target (Figure 8, c). Consequently, insertion of the selected functionalities near the carboxylate ester moiety should result in an enhanced cleavage rate because of transition state stabilization.

In an initial set of competition experiments between hydrazide **A** (Girard's reagent T) and neutral phenylacetic hydrazide **B**, we indeed observed a 70:30 ratio for hydrazones **7A** and **7B** at thermodynamic equilibrium (Figure 9).[61] Confirmation that this disproportion resulted from a stabilizing interaction between the ammonium and phosphonate groups came from the observation that the identical competition experiment using 2-methoxybenzaldehyde **8** (lacking the target) gave the corresponding hydrazones **8A** and **8B** in a 50:50 ratio. Additional proof for the occurrence of an intramolecular interaction came from the observation that no amplification was observed in case a large excess of hydrazide **A** was added or in case the equilibrium studies were performed at high building block concentrations. Under these conditions, the intramolecular interaction is outcompeted by the intermolecular interaction between phosphonate and free hydrazide **A**. In fact, maximum amplification was observed at dilute concentrations which favour intramolecular recognition events.

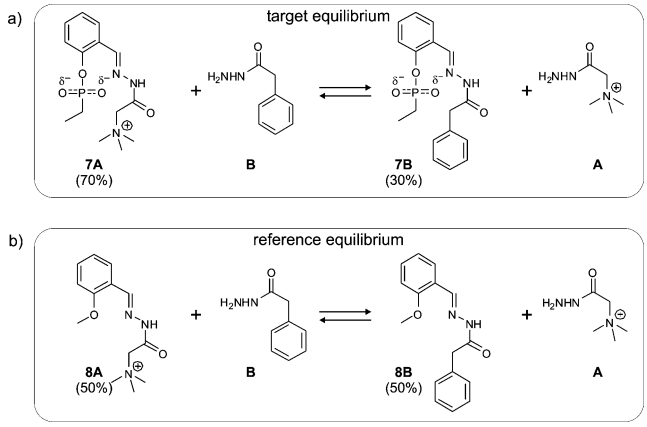

Figure 9. Intramolecular interactions between the phosphonate target and the ammonium group are identified from the product distribution in two competition experiments between hydrazides **A** and **B** in the presence (a) and absence (b) of target.

3.2. Screening via ^{1}H-^{13}C HSQC Spectroscopy

Besides illustrating the best experimental conditions, these initial studies also demonstrated the ease at which information on the occurrence of intramolecular interactions can be obtained. The simple integration of the characteristic signals of the hydrazones in the imine region (8–9 ppm) of the ^{1}H NMR spectra is sufficient to determine the equilibrium constant and comparison between the phosphonate- and methoxy-scaffold immediately returns an amplification factor. However, the screening of a library of hydrazides, rather than just two, is not straightforward. Com-

plications arise because of signal overlap in the ^{1}H NMR spectrum which complicates signal quantification. Additionally, the assignment of signals to the different members of the DCL requires those components in pure form as reference. Bidimensional ^{1}H-^{13}C HSQC spectroscopy can resolve the first problem by projecting the signals in two dimensions, but in its conventional form cannot tackle the second. In collaboration with the group of Damien Jeannerat, we have developed a protocol that eliminates the problem of signal assignment and allows for a real-time monitoring of a dynamic molecular system with a series of quick and highly resolved ^{1}H-^{13}C HSQC NMR experiments.[62] Kinetic ^{1}H-^{13}C HSQC NMR measurements become possible by using a spectral width in the ^{13}C dimension optimized for the carbon "fingerprint" area of the individual hydrazones (≈ 142–147 ppm). This reduces the number of time increments needed to resolve the signals by one or two orders of magnitude and, as a consequence, also the experimental time (which is in the order of 8 min).[63]

A key issue of the experimental set up is the gradual increase in complexity of the chemical system. Hydrazides **A**, **C** and **D** were added sequentially to the starting hydrazone **7B** and after each addition the system was let to equilibrate for 4 hours before a new hydrazide was added. After three additions, the final network was established, comprising 4 hydrazones and 4 hydrazides involved in a total of 12 exchange reactions (Figure 10). The appearance of new signals after each addition unequivocally allowed assignment of these signals to the newly formed hydrazones (**7A**, **7C**, and **7D**, respectively) (Figure 11, a). The changes in signal intensities of each species could be followed kinetically giving rise to the concentration profile of each species as a function of time depicted in Figure 11 (b). From this profile a wealth of information regarding the kinetic and thermodynamic parameters of the exchange reactions could be extracted. Second-order rate constants for all exchange reactions could be accurately determined and were within the range of 1.7–48.7 × 10^{-4} l mol^{-1} s^{-1} with a maximum error smaller than 10%. Additionally, extrapolation of the kinetic profile gave the possibility to calculate the network distribution at thermodynamic equilibrium, which ranks the hydrazones in terms of thermodynamic stability. The ability to monitor changes in the final network was illustrated by diluting the mixture 8 times. In accordance with previous observations[61] that concentration affects the equilibrium composition due to the competition between intra- and intermolecular recognition events, we indeed observed the amplification of hydrazones **7A** and **7D** on the account of **7B** and **7C**.

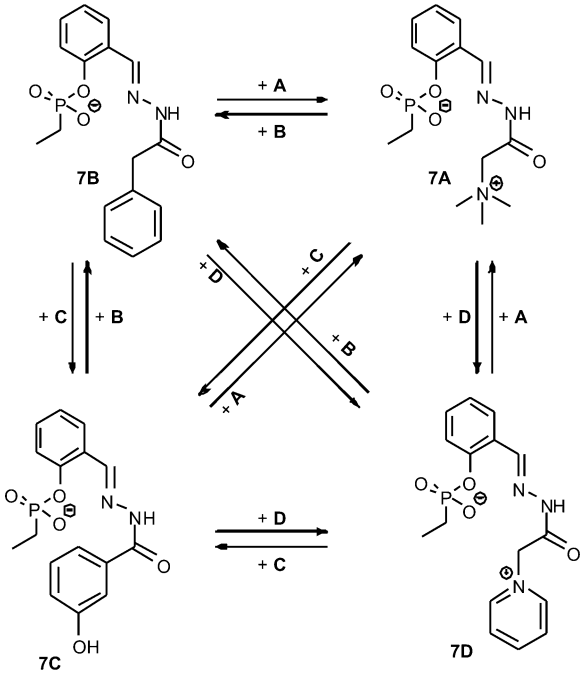

Figure 10. Chemical system studied by kinetic ^{1}H-^{13}C HSQC NMR measurements. Reprinted with permission from ref.[62]

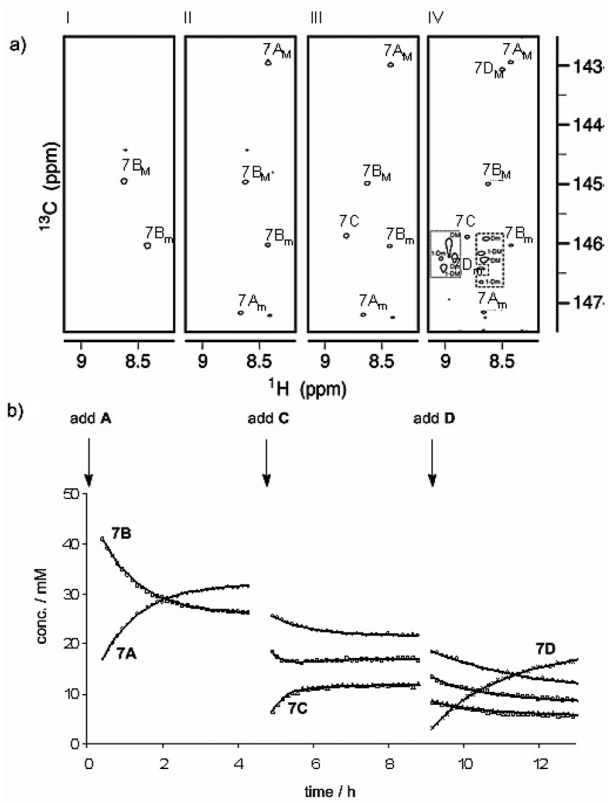

Figure 11. (a) ^{1}H-^{13}C HSQC NMR spectra (600 MHz, CD_3OD, 303 K) of the "fingerprint" area at different times (I: t = 0, II: t = 4, III: t = 8, IV: t = 13 h corresponding to the kinetic profile). (b) Concentrations of hydrazones **7A**, **7B**, **7C**, and **7D**. Reprinted with permission from ref.[62]

3.3. Screening via UV/Vis Spectroscopy

NMR spectroscopy is probably the most informative analytical tool for studying complex chemical networks, since it is one of the few techniques that allows a direct identification and quantification of all species present in solution as a function of time. The application of bidimensional NMR techniques is essential for assessing larger networks. Our experiments have illustrated that the performance of such measurements in small time intervals has significant advan-

tages in terms of compound identification and the assessment of the kinetic and thermodynamic parameters of the network. Nonetheless, inherent limitations of NMR spectroscopy include the requirement for relatively high sample concentrations and the use of sophisticated instrumentation (600 MHz equipped with TXI-cryoprobe). For those reasons we decided to develop also a methodology based on UV/Vis spectroscopy that would allow us to extract the desired information from a simple absorbance measurement.[64] The focal point of our studies is the determination of the thermodynamic stability of hydrazones relative to a reference hydrazone. No particular structural properties are requested for this reference, which means it can be chosen such that it has the ability to generate a unique UV/Vis absorbance. In this study we decided to choose hydrazide **E** as a reference inspired by the observation of Herrmann, Lehn et al. that reaction of **E** with *trans*-cinnamaldehyde **9** resulted in the formation of hydrazone **9E**, which has a highly characteristic UV/Vis absorption spectrum resulting from its conjugated push-pull system.[65] This is very useful, because it allows quantification of the concentration of **9E** in the presence of other species simply by measuring the absorbance at 348 nm. Knowing the concentration of **9E** implies knowing the concentrations of all other species through the use of mass balances, which thus allows the calculation of the equilibrium constant.

The experimental setup involved an initial competition experiment between the reference hydrazide **E** and the hydrazide of interest (Figure 12). After reaching thermodynamic equilibrium, an excess of *trans*-cinnamaldehyde **9** was added which quantitatively converted the remaining amount of hydrazide **E** into hydrazone **9E** (and **A** into **9A**). Comparison of the UV absorbance at 348 nm with a calibration curve for **9E** then returned the concentration of **9E** (and thus **E**). The general applicability of this strategy was illustrated by examining the thermodynamic stabilities

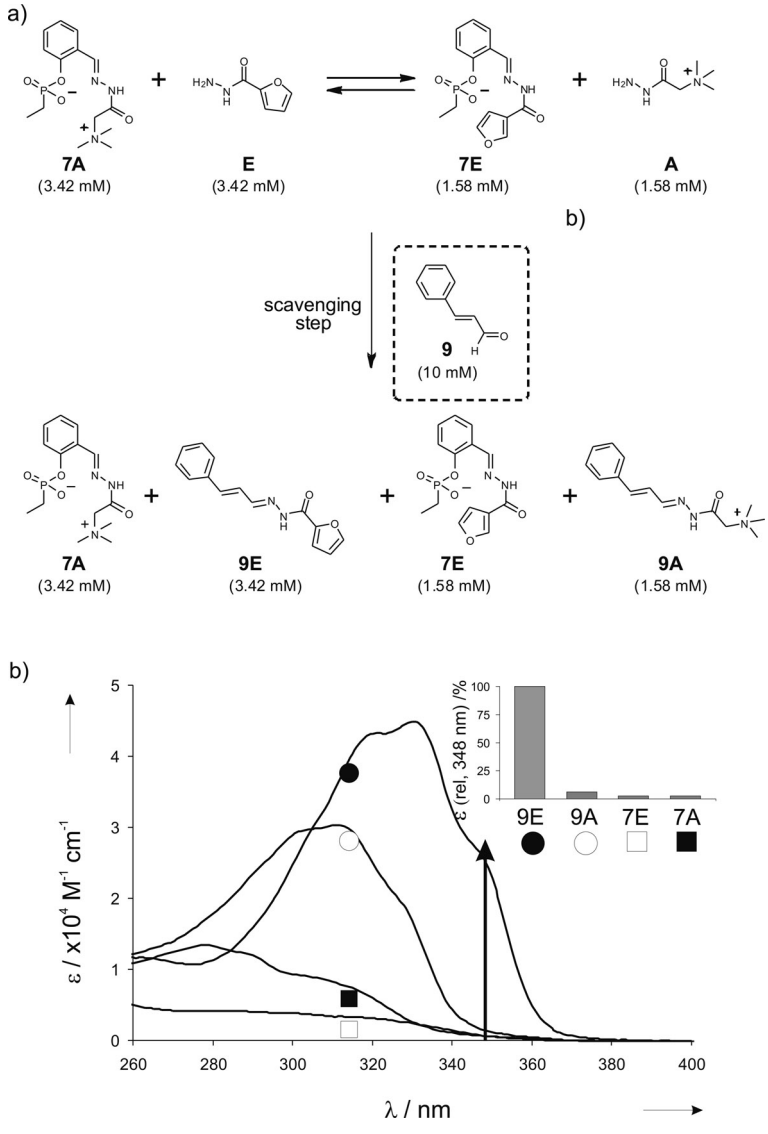

Figure 12. (a) Detection protocol for the analysis of the thermodynamic equilibrium between hydrazones **7A** and **7E** based on the scavenging of unreacted hydrazides with *trans*-cinnamaldehyde **9**. (b) UV/Vis spectra of hydrazones **7A**, **7E**, **9A**, and **9E**.

of a series of hydrazones, which yielded the same results as determined in a direct manner from ^{1}H NMR spectroscopy.

This protocol has the advantage of being simple, fast and accurate, but the main advantage is the disconnection between the structure of the target and the output signal. This implies that the latter can be optimized independently.

3.4. Self-Selection of Catalytic Units

Having at hand methodologies for the assessment of equilibrium constants, the attention was re-focussed on the key question: does a correlation exist between the functional groups self-selected by the phosphonate target and the ability of these groups to assist in the cleavage of a carboxylate ester? We examined a nine-component library of commercially available hydrazides equipped with functional groups potentially capable of interacting with the phosphonate group (apart from hydrazide **B** which served as a reference) (Figure 13, a).[66] The thermodynamic stabilities of the hydrazones formed upon reaction with either phosphonate-target containing scaffold **7** and reference scaffold **8** were all related to the reference hydrazones **7B** and **8B**, respectively. Any increase in thermodynamic stability using scaffold **7** with respect to scaffold **8**, expressed in amplification factors, was ascribed to a stabilizing interaction between the functional group present in the hydrazide and the phosphonate group (Figure 13, b). These experiments identified the occurrence of an intramolecular interaction in compounds **7A**, **7D**, and **7F** (in the order **7A** > **7D** ≈ **7F**) (Figure 13, b). Based on these results, phenyl acetates **10A**, **10B** (which served as a reference) and **10F** were prepared in which the structural elements of hydrazides **A**, **B**, and **F**, were positioned in close proximity to a neighboring carboxylate ester (Figure 14). Hydrazides **A** and **F** were studied in detail as these express a different type and strength of interaction with the transition state (electrostatic and H-bonding, respectively). Measurement of the methanolysis rates of **10A**, **10B**, and **10F** gave pseudo-first-order rate constants ($k_{obs,\mathbf{10A}} = 3.96 \times 10^{-2}$ s^{-1}, $k_{obs,\mathbf{10F}} = 1.82 \times 10^{-2}$ s^{-1}, and $k_{obs,\mathbf{10B}} = 0.82 \times 10^{-2}$ s^{-1}) in perfect agreement with the results of the amplification studies, both in terms of the order of reactivity ($k_{obs,\mathbf{10A}} > k_{obs,\mathbf{10F}} > k_{obs,\mathbf{10B}}$) and the relative acceleration (4.8:1.6:1). A series of control experiments gave strong support for the hypothesis that rate acceleration resulted from transition state stabilization.

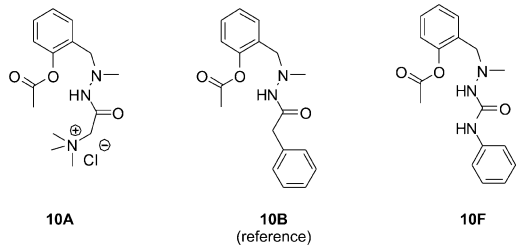

Figure 14. Functionalized phenylacetates **10A**, **10B**, and **10F**.

These initial results are important, because they establish a correlation between the thermodynamic amplification in the dynamic system and the efficiency of the selected chemical function in assisting in intramolecular catalysis. So far, the dynamic covalent capture approach has allowed the self-selection of functional groups that assist in intramolecular catalysis, but these are not yet catalysts. Current efforts are aimed at developing true catalysts by performing a second self-selection cycle aimed at catalyzing the first steps leading towards formation of the covalent intermediate.

The examples of our group and others discussed in this section illustrate the potential of dynamic combinatorial chemistry and, more specifically, dynamic covalent capture[6] as a tool for catalyst discovery. These are exciting and promising results, but it is evident that the road towards the isolation of highly active catalysts is long. A critical hurdle which has to be taken regards the size of the dynamic libraries. Apart from some exceptions,[67,68] most DCC studies are proof-of-principle studies involving relatively small

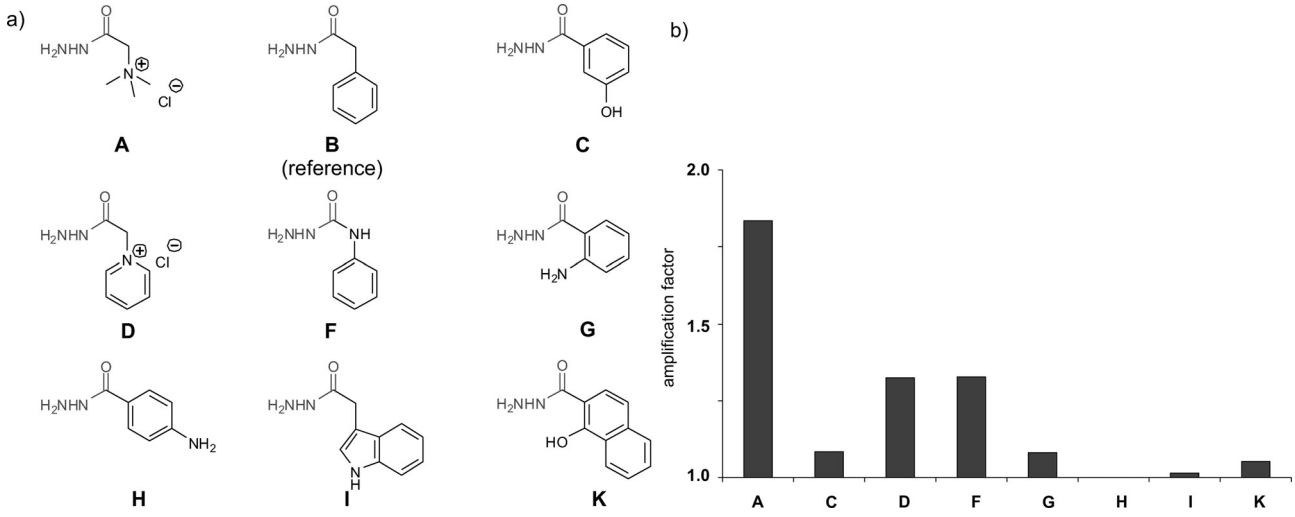

Figure 13. (a) Hydrazide library and (b) observed amplification factors with respect to reference hydrazide **B**.

libraries with a limited structural diversity between the members. It is hard to get something really astonishing from libraries of this size. The development of analytic tools that permit the preparation and screening of large, structurally diverse libraries is of key importance. The second critical issue is of more fundamental nature and concerns the use of transition state analogues (TSA) as targets for identifying catalysts. Although this approach is also commonly used for the development of catalytic antibodies and molecular imprinted catalytic polymers, it bears the intrinsic disadvantage of requiring knowledge about the molecular structure of the transition state. By itself this is not problematic, but simply puts limits to the type of reactions that can be addressed with this approach. More importantly, the a priori focusing on a given transition state excludes the identification of maybe superior catalysts that work through unforeseen alternative mechanisms. Future investigations will have to tell to which extent these issues will actually pose limits to the applicability of DCC-based methodology for catalyst discovery.

4. Self-Evolving Catalysts

Traditionally, organic chemists consider a mixture of molecules as a half-done job; separation, isolation and the individual analysis of each components is a must. This is in sharp contrast with Nature, which achieves its tasks through complex networks of molecules regulated by feedback loops and control mechanisms. These networks are highly dynamic in nature, which generates adaptability to changes in the environment. The most intriguing aspect is that these ensembles of molecules have properties that cannot be traced back to a single component. Since long, it has fascinated chemists to understand at which point a set of molecules gives rise to the most important emerging property of all, which is life.[69] In this respect, the ability of molecules to self-replicate is one of the essential issues and numerous minimal artificial self-replicating molecules have been reported and extensively reviewed.[45,70–72] Without entering in that specific area, these studies have recently lead towards the definition of a new research area in chemistry, called systems chemistry.[73,74] Systems chemistry actively pursues emerging properties of whatever kind in mixtures of synthetic molecules. So far, studies have mainly focussed on networks of replicating molecules because related to the fundamental question of how life originated on Earth.[75,76] Within the context of dynamic catalyst discovery, it can be envisioned that systems chemistry may ultimately lead to the development of "smart mixtures" able to catalyse (a cascade of) chemical transformations induced by a trigger event, which is the addition of reagents. Systems chemistry has not yet reached the level of sophistication to propose networks of this type, but the following examples shed some light on this potential.

Philp and Sadownik recently reported on the self-amplification of a replicator from a dynamic reagent pool.[77] In this elegant study, they coupled the dynamic exchange in a small library with the irreversible formation of a self-replicator able to shift the library composition in its own favour. A minimal four-component dynamic library composed of imines **11M** and **12M** and nitrones **11L** and **12L** was obtained upon mixing aldehydes **11** and **12**, hydroxylamine **L**, and amine **M**. Previous studies had shown that the nitrones **11L** and **12L**, but not the imines, are able to undergo a 1,3-dipolar cycloaddition reaction with maleimides.[78] Thus, the addition of reference maleimide **13a** opens up a gateway

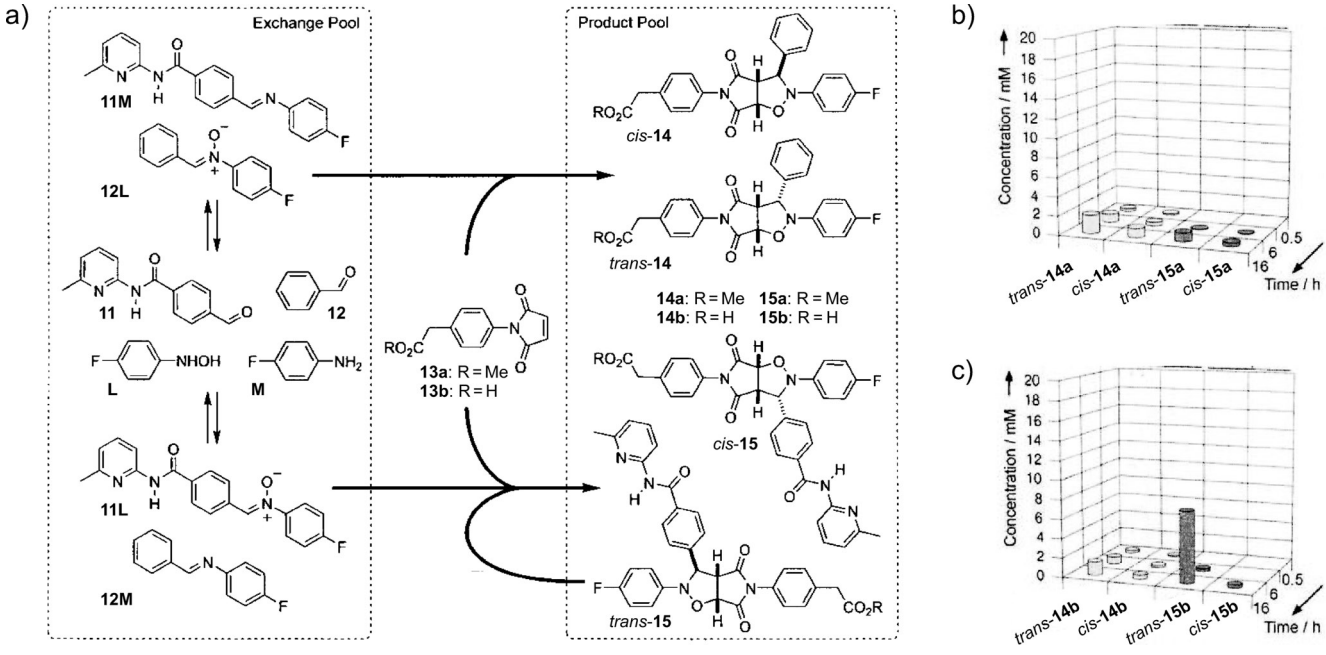

Figure 15. (a) Self-amplification of a replicator from a dynamic imine/nitrone library. Distribution in the product pool using either (b) reference maleimide **13a** or (c) maleimide **13b** able to form the self-replicator *trans*-**15b**. Reprinted with permission from ref.[77]

to irreversibly funnel compounds **11L** and **12L** into a product pool, yielding two pairs of diastereomeric cycloadducts: *cis*- and *trans* **15a** and *cis*- and *trans*-**14a**, respectively (Figure 15, a). Product formation was rather unselective and after 16 hours, the *cis*- and *trans*-isomers of **14a** were present at 3 mM and those of **15a** at 1.4 mM, reflecting the higher initial concentration of **12L** compared to **11L** (Figure 15b). The total conversion into product was not more than 21%. An entirely different scenario was observed when maleimide **13b** was added. At difference with the reference maleimide, **13b** has a free carboxylic acid moiety able to form a hydrogen-bond complex with the amidopyridine unit in **11L**. Furthermore, this complex is complementary to the *trans*-diastereoisomer of **15b**, which thus acts as a template for its own formation through the ternary complex [**11L**·**13b**·*trans*-**15b**]. This catalytic complex causes a 100-fold rate acceleration of the cycloaddition reaction between **11L** and **13b**. In this system a preferential pathway is present that converts nitrone **11L** selectively in *trans*-**15b**. Importantly, the rapid depletion of this compound drives the dynamic library towards the formation of more **11L**, which means that the auto-amplification is a progressive process. The consequence is a dramatically different distribution in the product pool. After 16 hours, replicator *trans*-**15b** now made up almost 80% of the products (against 22% for the reference system) with a total conversion of 48% (Figure 15, c).

Independently, Xu and Giuseppone combined self-replication and the reversibility of dynamic combinatorial chemistry in a completely different system.[79] Inspired by the well-known self-replicating molecules of Rebek,[80] "dynamic" analogues were prepared in which the amide bond was replaced by an imine. The ability of one of the library members to self-duplicate caused its amplification (up to 83%) compared to the expected value based on a statistical distribution.

5. Conclusions and Outlook

Supramolecular catalysis has been around since the birth of supramolecular chemistry, but is witnessing a renaissance as a result of some recent developments. An important factor is that chemists working with classical organometallic catalysts got interested in designing new catalysts based on noncovalent interactions. This has caused a shift from bio-inspired systems towards systems based on catalysts that already have abundantly proven their industrial applicability. Consequently, this has significantly widened the scope of supramolecular catalysis, has increased the general interest in their development and has brought the application of these systems much closer. From the examples discussed in this review it is evident that the dynamic approach towards catalyst discovery is now a vibrant mix of several disciplines. Apart from supramolecular and organometallic chemists, analytical chemists are involved in developing dedicated tools for studying the interactions within more and more complex systems. The study of such complex networks will benefit from the input of biochemists involved in systems biology.

The emergence of dynamic combinatorial chemistry and systems chemistry has conceptually changed the way in which catalyst discovery can be approached. Dynamic combinatorial chemistry has all to do with the creation of potential. Virtual libraries can be easily generated that can cover a large amount of chemical space. The ability of these libraries to spontaneously adapt to a stimulus allows for self-selection which partly relieves the burden of rational catalyst design. Systems chemistry breaks the ban of studying mixtures rather than pure compounds, which is potentially very interesting from the viewpoint of catalyst discovery. An integrated approach including evolving dynamic combinatorial libraries and an extensive use of recognition motifs for self-assembly of the catalyst, the substrate *and* the transition state will lead to unprecedented catalytic systems.

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