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Challenges in the development of organic and hybrid molecular systems

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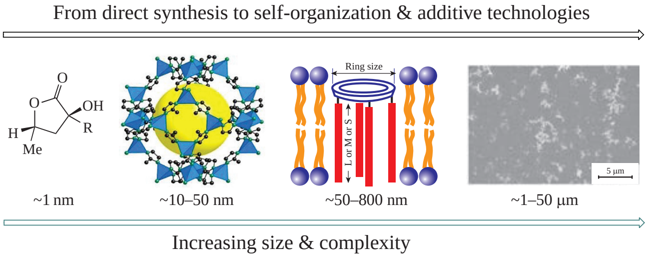
The rapid development of organic chemistry and catalysis has provided outstanding chemical tools to build complex molecular architectures that were never possible before. In spite of amazing progress in studying individual molecules and reactions, practical applications are limited due to the high cost of newly developed technologies and the difficulty in understanding the processes at the molecular level. Herein, we summarize our first steps and experiences carrying out an ongoing project on organic and hybrid molecular systems that highlights new fascinating opportunities and identifies future challenges.



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Introduction

Conceptual breakthroughs described in recent decades have substantially influenced our understanding of reactions and processes involving organic molecules. The unique capability to manipulate molecules and matter,[1] new concepts in reaction discovery,[2] the transition from biochemistry and nanotechnology to neuroscience,[3] and chemical interactions in microbiomes[4] – just to name a few. Tuning the molecular complexity and the synthesis of complex organic molecules with atomic precision have emerged in response to the increased demand for new organic molecules.[5–7]

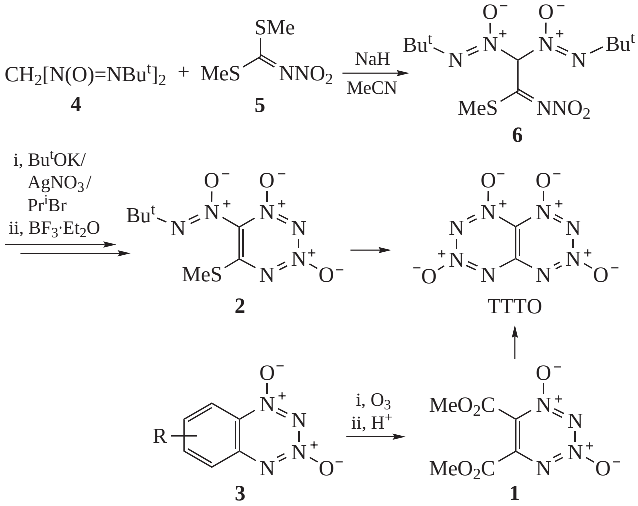
The rapid exploration of new areas of modern science would not be possible without paramount instrumental development of analytical methods and high-end research hardware. Many sophisticated analytical methods that were difficult to use in the past have now become routine toolboxes.[8] Incorporating cutting edge analytical tools based on NMR spectroscopy, mass spectrometry and electron microscopy into everyday research practices has provided important insight into previously impossible to resolve mechanistic questions. A target-oriented approach directed the efforts toward the construction of a universal system for performing mechanistic studies.[9]

Recently, we have launched an initiative to develop rational concepts for designing new organic and hybrid molecular systems in view of creation of practical technologies and sustainable development.[10] An attempt to define a unified concept to access complex molecular architectures has identified a few key-points that are critical for progress in this area. This is not a regular literature review; instead, in this focus article, we briefly summarize the experiences gained as we make progress with the ongoing project and discuss challenging problems that may be solved in the near future. We believe that the discussion of future challenges is needed to stimulate research in this area.

Small organic molecules

A rational algorithm for developing organic and hybrid molecular systems commonly includes the consecutive building of molecular complexity *via* the step-by-step combination of relatively simple structural fragments into more complex hierarchical structures. It is based on organic synthesis as a power tool for the formation of chemical bonds between these fragments. From a number of the known synthetic approaches, those are preferable that allow putting together starting units selectively, while keeping the other functional groups unchanged. Furthermore, novel, efficient, and environment-friendly fine catalytic methodologies that would not produce waste when used in industrial applications (atom-economy) are highly desirable.[11] In this section, some modern synthetic approaches to the formation (in particular, enantioselective formation) of carbon–carbon, carbon–heteroatom and heteroatom–heteroatom chemical bonds that substantially meet these criteria are briefly considered conformable to different types of relatively small, practical organic molecules.

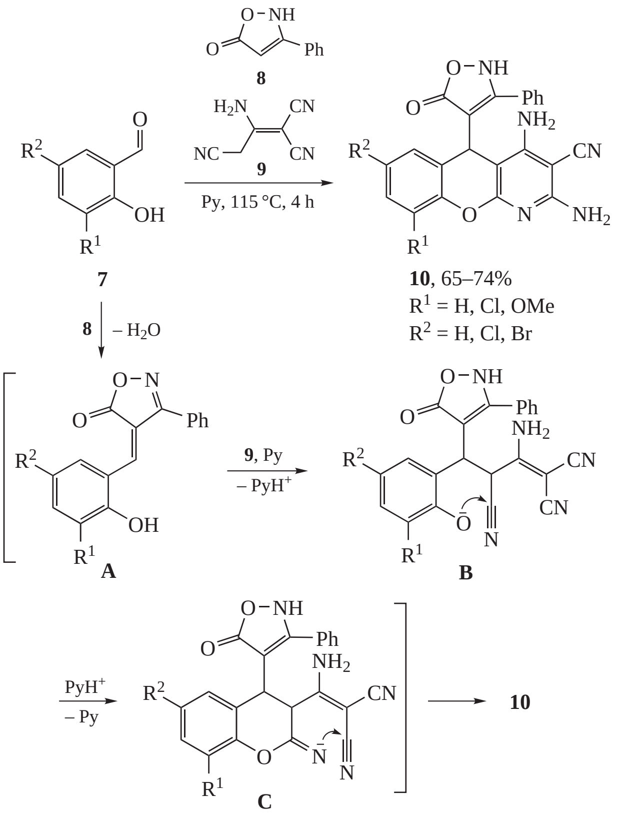
The first example relates to 1,2,3,4-tetrazine 1,3-dioxides – a perspective class of polynitrogen organic compounds with an unusual combination of alternated nitrogen atoms and *N*-oxide fragments.[12] According to theoretical studies, hypothetical tetrazinotetrazine 1,3,6,8-tetraoxide (TTTO), which belongs to this class, should be ranked among the most powerful explosives.[13] Furthermore, due to the presence of the unique system of semi-polar nitrogen–oxygen bonds, TTTO may act as an efficient NO-donor for medicinal applications.[14] Recently, interesting synthetic approaches to compounds **1** and **2**, which are considered to be close precursors to TTTO, have been proposed (Scheme 1). Precursor **1** was synthesized by the cleavage of the aromatic ring in the benzotetrazine 1,3-dioxides **3**[15] bearing electron-donating substituents with ozone, followed by the acidic treatment of the primary reaction product (Scheme 1).[16] The synthetic strategy used to create compound **2** included coupling bis(*tert*-butyl-NNO-azoxy)methane **4** with dimethyl nitrodithioimidocarbonate **5** in the presence of NaH to create *N*-nitroimine **6**, and then compound **6** was transformed to the target molecule **2** with a sequence of O-alkylation and ring closing reactions.[17] This strategy led to the formation of new C–C and N–N bonds in compound **2** bearing *ortho*-located diazene-*N*-oxide and methylthio groups, which were needed for further target-oriented synthesis. The X-ray diffraction studies of **1** and **2** confirmed the crystal structures of these important molecules. The next and most challenging step will be the conversion of **1** and **2** to TTTO. It is expected that the synthesis of TTTO would experimentally confirm the theoretical hypotheses and provide a clue as to how to prepare other prospective nitrogen-oxygen systems.[18]



Scheme 1

The most impressive trends in modern organic synthesis are the domino and cascade reactions that allow one to achieve a simple one-pot formation of two or more chemical bonds.[19] Among them, the multicomponent reaction strategy has sufficient advantages over conventional step-by-step synthesis due to its flexible, convergent and atom efficient nature.[20] Recently, a convenient one-pot multicomponent synthesis of 5-C-substituted chromeno[2,3-*b*]pyridines **10** from salicylaldehydes **7**, 3-phenylisoxazol-5(4*H*)-one **8** and malononitrile dimer **9** was reported (Scheme 2).[21] The best yield of product **10** was attained in boiling pyridine, which served as a solvent and a mild base simultaneously. The cascade process was most likely started by Knoevenagel condensation between aldehyde **7** and carbon acid **8**, followed by the subsequent reaction of **9** with adduct **A** to afford anion **B**. Then, two intramolecular cyclizations of intermediates **B** and **C** completed the synthesis of target molecule **10**. In total, four new chemical bonds (two C–C, one C–O and one C–N) were formed during this interesting pot, atom and step economy (PASE) transformation. The prepared functionalized chromeno[2,3-*b*]pyridines are analogues of the known protein kinase 2 inhibitors and compounds that suppress the expression of TNFα and U937 cells.[22]

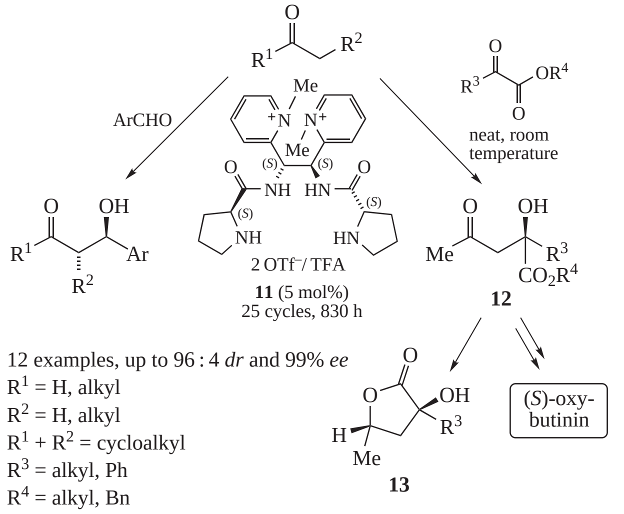
Over the past decade, excellent opportunities for the design of practical and important organic and hybrid molecular systems have been offered by intensively developing methodologies of asymmetric organocatalysis.[23] In the presence of small metal-free chiral organic molecules (α-amino acid or cinchona alkaloid derivatives, BINOL phosphoric acids, and other types of chiral molecules), available prochiral and racemic reagents can be easily converted into chiral products of high molecular complexity in high yields and with excellent enantioselectivities. However, the majority of organocatalysts are substantially less active than organometal catalysts and enzymes due to the absence of an activator metal. These expensive (especially for the 'unnatural' configuration of stereocenters) and difficult-to-recycle chiral compounds should be used in an amount of up to 30 mol%, which significantly limits their application in the pharmaceutical industry. Therefore, the development of simple, active and sustainable organocatalysts and catalytic systems is still a challenge.[24]



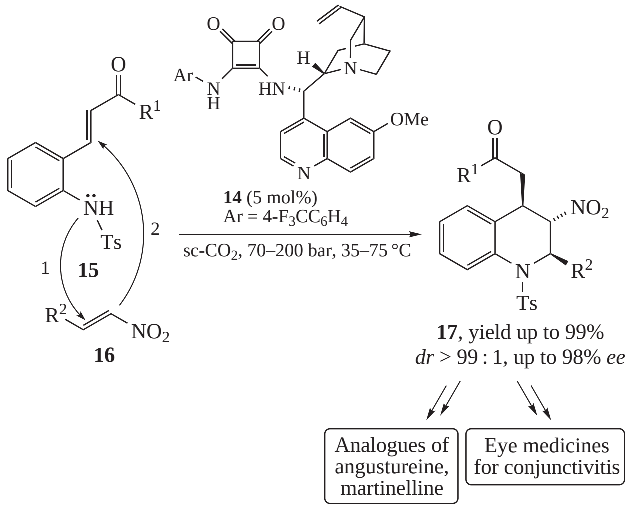
Scheme 2

Recently, a novel approach to solve this problem has been proposed. It is based on the linkage of two chiral catalytically active fragments using the C_2-symmetrical (1,2-diaminoethane-1,2-diyl)bis(*N*-methylpyridinium) group.[25] This group not only facilitates catalyst recovery by creating a heterogeneous reaction environment but also plays an important role in the stereoselection process. This pattern has produced the highly recyclable organocatalyst **11** for asymmetric cross-aldol reactions in ketone–ketone, ketone–aldehyde, and aldehyde–aldehyde systems under neat conditions (Scheme 3). The reaction products, chiral α-hydroxy γ-keto esters **12**, are useful precursors to the natural compound analogues **13** and active pharmaceutical ingredients.[26] The novel catalyst retained high activity and excellent stereoselection over the more than 830 h operating period. Hopefully, (1,2-diaminoethane-1,2-diyl)bis(*N*-methylpyridinium) and similar C_2-symmetric chiral fragments[27] would be a suitable platform for designing a series of highly efficient recyclable hybrid catalysts for various asymmetric reactions, including those that produce pharmacology-oriented organic nitrogen-oxygen systems.

On the other hand, C_1-symmetrical bifunctional chiral diamines may serve as efficient catalysts of asymmetric cascade (domino) PASE reactions, which are considered an extremely prospective approach to the synthesis of complex enantiomerically enriched compounds.[28] These reactions are even more attractive from the green chemistry viewpoint when inflammable, non-toxic and easy-to-evaporate dense gases are used as the reaction media.[29] Among them, carbon dioxide, an available natural gas with a low critical point (31.1 °C/73.8 bar), attracts considerable attention and has many applications for catalytic[30] and, particularly, organocatalytic reactions.[31] Recently, the first asymmetric organocatalytic domino reaction in a supercritical (sc) fluid was reported. In the presence of bifunctional quinine-derived squaramide **14**, *o*-(*N*-tosylamino)phenyl α,β-enones **15** reacted with α-nitroalkenes **16** in the sc-CO_2 medium to create pharmacological tetrahydroquinolines **17** with very high diastereo- and enantioselectivity *via* the one-pot domino sequence of intermolecular N-Michael (1) and intramolecular C-Michael (2) steps (Scheme 4).[32] The tetrahydroquinoline fragment is an integral part of a number of natural and artificial bioactive compounds. Among them is angustureine, which was isolated from the bark of a South American tree, *Galipea officinalis*; it exhibits anti-mycobacterial and anti-malarial activities.[33] Martinellic acid and martinelline, extracted from the tropical plant, *Martinella iquitosensis*, are potent antagonists of bradykinin receptors and are used as an eye medicine to treat conjunctivitis.[34] Other applications of dense gases and sc-fluids to asymmetric organocatalysis may result in the development of novel resource-saving and environment-friendly technologies[35] for the industrial production of enantiomerically pure active pharmaceutical ingredients.[36]



Scheme 3



Scheme 4

Bioorganic molecular and hybrid systems

The highest level of complexity and variable functionality was found in the bioorganic frameworks that stimulate interdisciplinary studies of 3D molecular systems bearing synthetic and natural bioorganic ligands, including proteins and oligopeptides, oligosaccharides and polysaccharides (often referred to as glycocompounds), steroids, and lipids, among others.[10] During the past year, key attention within discussed project was paid to the synthesis of glycoligands and glycoscaffolds and further design of molecular systems that were directly related to the development of novel drugs, vaccines and diagnostic systems.[37–39] A critical step in the preparation of oligosaccharide compounds relates to the stereoselective construction of glycoside bonds, and first of all of glycoside bonds with 1,2-*cis*-stereochemistry. The results of the detailed investigation of the stereocontrolling effects of remote *O*-acyl substituents[40] have been summarized in reviews[41,42] and applied to the assembly of penta-[43] and longer homo-α-(1→3)-oligoglucosides related to α-(1→3)-glucan of *Aspergillus fumigatus*. They were obtained within the program with the systematic syntheses of key fungal cell wall carbohydrate antigens, particularly the oligo-β-D-mannooligosaccharides[44] related to the antigenic factor 6 of *Candida* (see structures **28**, **31**, **33**, **35** and **37** in Figure 1), and 2-amino-2-deoxy-α- or -β-D-galactopyranosylated structures prepared *via* a novel synthetic approach based on glycosylation by phenyl 2-azido-2-deoxy-1-seleno-α-D-galactopyranoside derivatives.[45]

Recently, there has been a special interest in the development of a straightforward synthesis of hybrid glycostructures that have carbohydrates and other functionalities as potential pharmacophore groups. In this context the syntheses were performed of first discovered pyridine α-nucleoside Neopetroside A from a marine *Neopetrosia* sp. The sponge and its β-riboside analogue[46] (Figure 2), as well as a series of cyanogenic glycosides, including

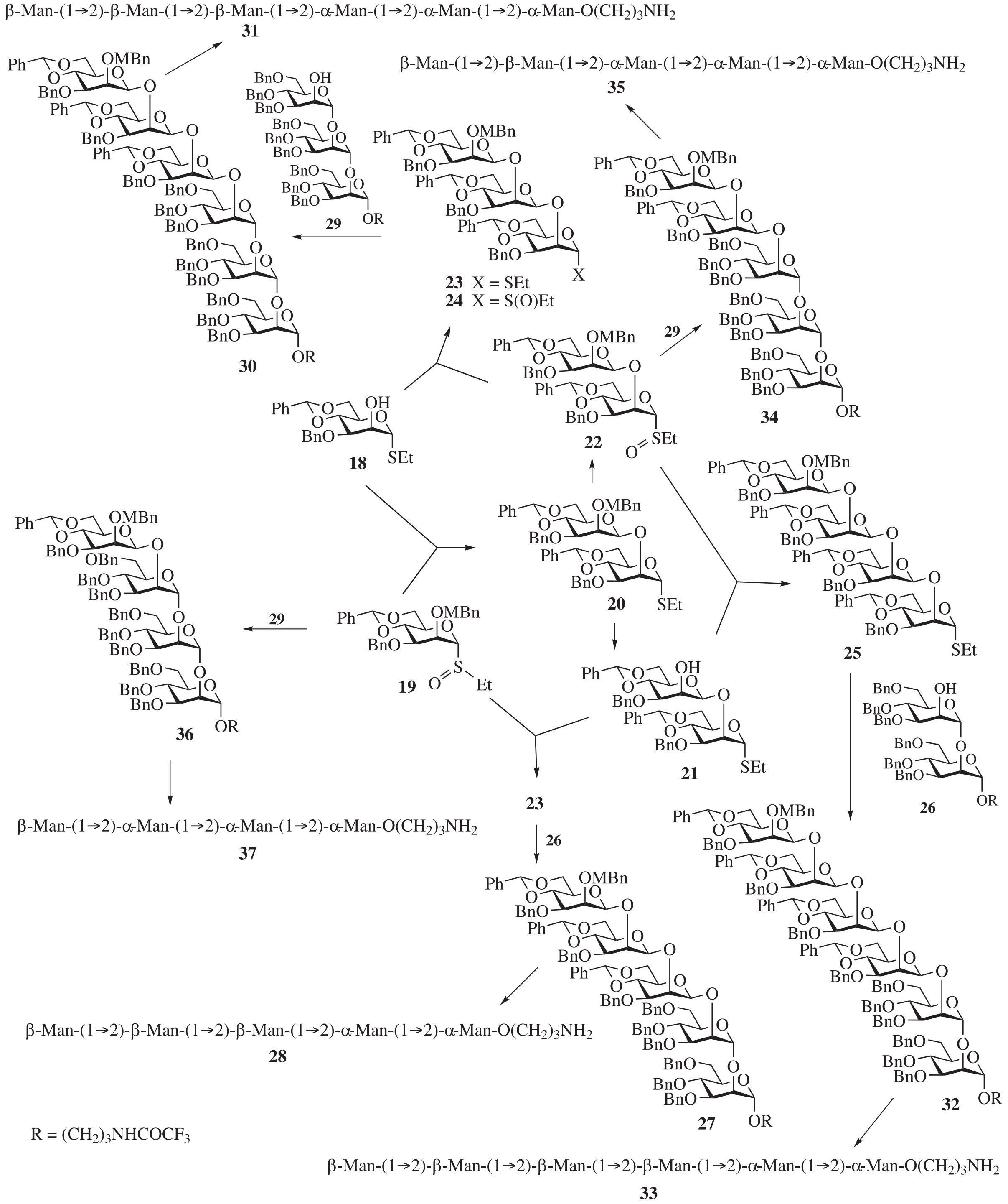


Figure 1 Principal scheme of the stereoselective assembly of oligo-β-D-mannooligosaccharides related to the antigenic factor 6 of *Candida*.

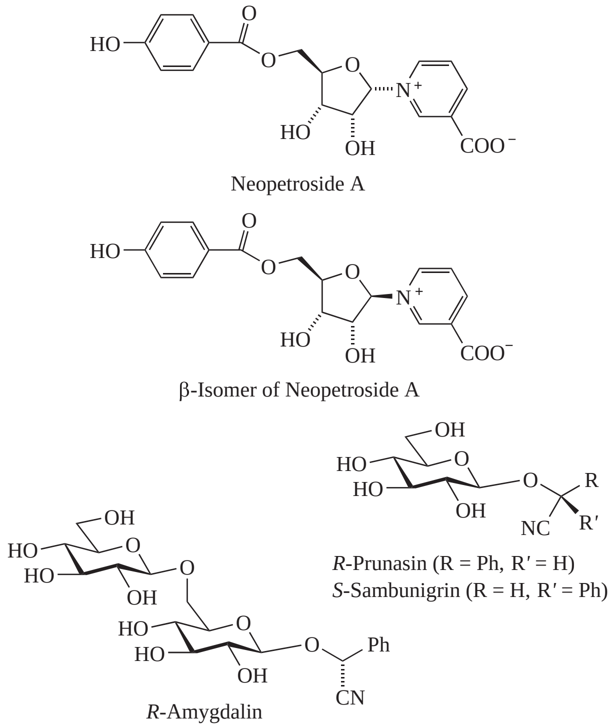


Figure 2 Structures of synthesized Neopetroside A, its β-isomer and natural cyanogenic glycosides.

R-prunasin, *S*-sambunigrin and *R*-amygdalin[47] plant toxins, are known as cyanogens. Neopetroside A exhibited a very promising profile of biological activity to serve as a basis for novel drug development. On the contrary, in spite of previous publications (for review see ref. 48), the cyanogenic glycosides, including most known of them – amygdalin, demonstrated low activity, which was surprising because such compounds are used in different traditional medicines, and amygdalin has been even found in the illegal anticancer market.

Another challenging aspect in the synthesis and investigation of biomolecular systems was connected to the design of oligodentate structures bearing a defined amount of repeated functional elements linked to low-molecular-weight scaffolds toward biomolecular systems with distinct structure and the desired 3D architecture. Recently proposed cyclooligo-β-(1→6)-D-glucosamines[49,50] can be regarded as the scaffolds of choice due to their optimal functionality and stereochemical organization. They were applied as the basis of blockers of oligodentate bacterial adhesins[51] and artificial ion channels.[52] Further studies in this direction permitted to design the exceptional examples of stable and selective artificial ion channels shown in Figure 3[53] in addition to other modern examples of molecular systems of this type.[54]

Natural polysaccharides are indispensable structural elements to design molecular systems. The practical use of sulfated seaweed polysaccharides, which exhibit a very high affinity to cellular receptors, is limited due to the structural irregularity of this type of biopolymer. That is why the development of reliable approaches for their transformation into regular structures is also challenging. In this context, an efficient method to transform irregular O-sulfated and branched fucoidan from *Punctaria plantaginea* seaweed into a per-O-sulfated linear analogue [Figure 4(*a*)] using a subsequent chemical treatment was proposed.[55] It provided a standard and easily characterized polymeric product that exhibited high anticoagulant activity possibly due to ability of the polymer to form a ternary complex with thrombin and ATIII that was demonstrated with computer modeling [Figure 4(*b*)]. The obtained linear polymer can be applied as drug substances,[56] a building block for designing more complex molecular systems of higher generation, and particularly as the ligands for contrasting agents for MRI, PET, and other diagnostic technologies.[57–59]

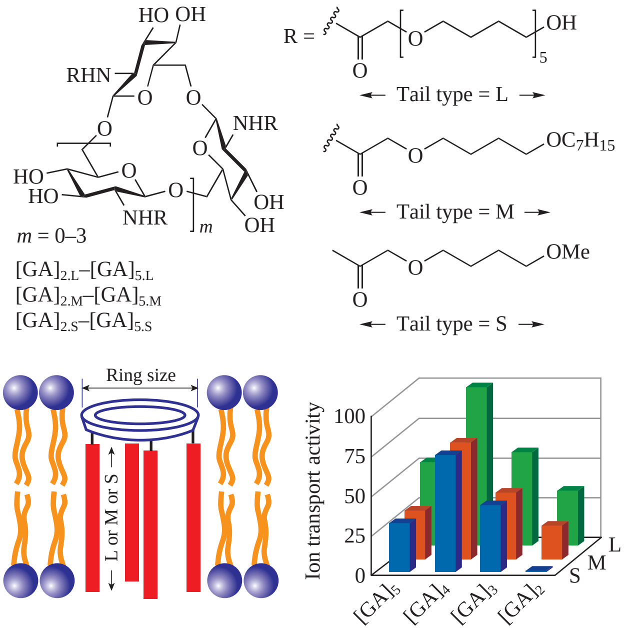


Figure 3 Principal scheme of artificial ion channel design and examples for their ion-selectivity.

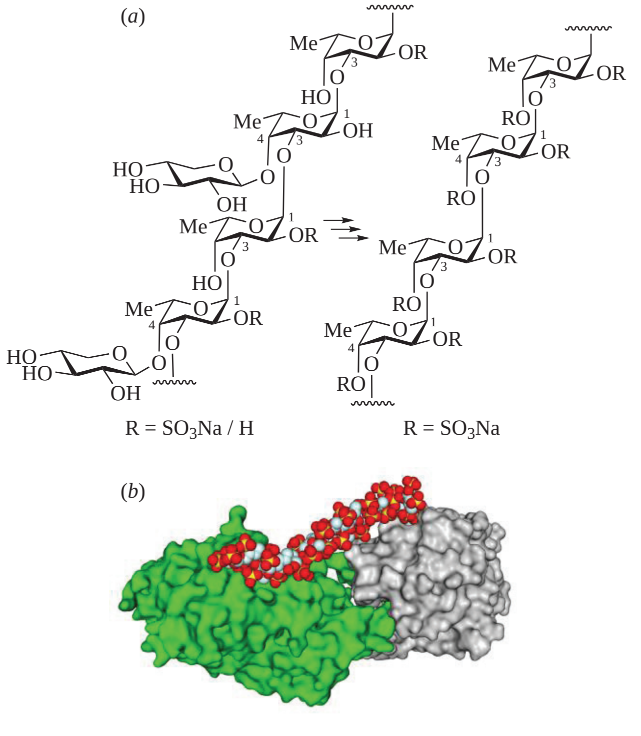


Figure 4 (*a*) Principal scheme for the chemical transformation of branched fucoidan from *P. plantaginea* seaweed into the linear and regular per-O-sulfated product and (*b*) the possible ternary complex between thrombin (gray), ATIII (green) and 18-saccharide fragment of the synthesized fucoidan.

Heterogeneous catalysis and surface science

Hybrid materials provide unique opportunities to demonstrate the synergy of the nano-sized components or even to gain new properties that have not been observed for the individual components that constitute the hybrid material. Among the wide range of hybrid materials, including purely inorganic systems, organo-inorganic materials and mixed organic structures that are currently designed to meet the growing demands of the modern applications, including catalysis, energy conversion/harvesting, and environmental protection, two material groups are of utmost interest. The first one represents metal organic frameworks (MOFs) or coordination polymers (including covalent organic frameworks) with surface areas reaching 5500 m^2 g^{-1} and pore volumes up to 2 cm^3 g^{-1},[60–62] and the second one incorporates core-shell bimetallic nanoparticles encapsulated in nano-porous materials.[63–65]

Metal organic frameworks in membranes

By studying the adsorption/separation of gases, membrane hybrid materials based on ceramic, metalloceramic or polymer starting membranes with a supported layer of MOFs or mixed matrix membranes (MOFs dispersed in a polymer matrix) that provide molecular recognition and selectivity and could distinguish between very similar molecules (like ethane/ethylene, N_2/CO_2 or CO/CO_2) can be designed and used. MOFs are usually synthesized by a solvothermal method that is time consuming (30–50 h) and yields non-uniform MOF particles. Microwave activation can improve the synthesis of MOFs. In this case, the time required for the synthesis can be reduced to 15–20 min, and uniform MOF nanoparticles are formed (*cf*. Figure 5).[66(*a*)] The microwave-prepared material was efficiently used as a catalyst for phenylacetylene hydroamination, an adsorbent for hydrocarbons or a component of membranes.

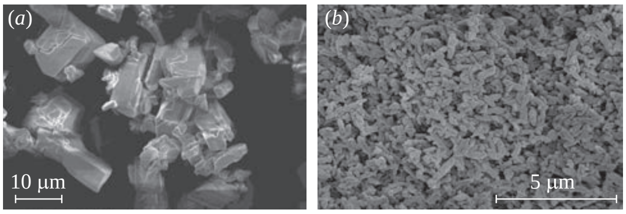


Figure 5 SEM images of (*a*) ‘solvothermal’ and (*b*) ‘microwave’ MIL-53(Al) samples.

Integrated membranes with a nearly ideal (no defects) layer of MOF onto the appropriate membrane were prepared *via* the one-step *in situ* synthesis by crystallization of MOF onto the membrane or by template synthesis using crystallization centers at the surface and secondary growth. Zeolite-like Zn-imidazolate framework (ZIF-8) and Cu-phenylenedicarboxylate framework (MOF-199) (Figure 6) were used to illustrate the approach.[66(*b*),(*c*)] Polyacrylonitrile was chosen as a matrix to support the MOFs because a homogeneous, uniform and smooth MOF coating was produced.[66(*d*)]

The permeance of ZIF-8/membrane materials changes in a different way depending on the nature of the starting membrane. The permeance to He decreases by a factor of 1.4 for the ZIF-composite compared to the starting membrane, whereas the permeance with respect to N_2 or CO_2 somewhat decreases so that the CO_2 selectivity increases significantly. For instance, for the He/CO_2 couple, the selectivity for ZIF-8/PAN is ~9.2, which essentially exceeds the theoretical (Knudsen) selectivity for this couple with porous membranes (Table 1).

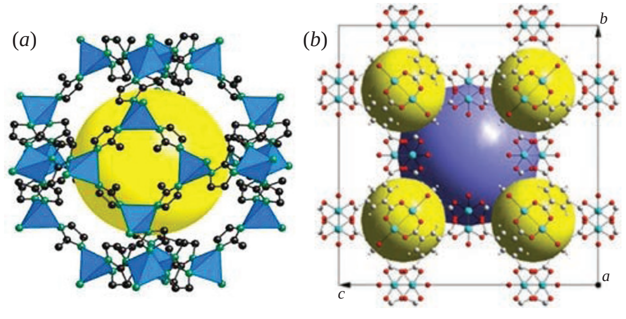


Figure 6 (*a*) Zn-imidazolate framework (ZIF-8) and (*b*) Cu-phenylene-dicarboxylate framework (MOF-199).

Table 1 Selectivity of ZIF-8 membranes.

Membrane	Selectivity			
	He/CO_2		He/N_2	
	α_{Kn} (theory)	α_{exp}	α_{Kn} (theory)	α_{exp}
PAN	3.3	2.0	2.6	2.2
ZIF-8/PAN	3.3	9.2	2.6	8.7

Mixed matrix membranes may be a breakthrough in the design of gas permselective membranes and MOF-modified polymers (PIM-1), which already demonstrated unique properties. The empirical selectivity *vs.* permeance dependence is known to obey the so-called Robeson law, *i.e.*, the experimental data are limited by a linear upper-bound curve. However, for the ZIF-8/PIM-1 membranes, the experimental points are over this limiting curve.

Core-shell nanoparticles encapsulated in nanoporous materials

Core-shell or decorated nanoparticles with tunable sizes and morphologies encapsulated into hierarchical matrices or structured carriers, represent unique hybrid materials for catalysts and other applications. The proper design of such hybrids will result in the enhancement of the activity, selectivity, stability and decreased production costs. Original procedures have been developed for the preparation of bimetallic Au/Me or Au/MeO_x catalysts by depositing Au through redox procedure on the surface of Cu, Pd, Pt, and Ru supported nanoparticles. Catalysts with a very low Au loading of < 0.2 wt% and particle size of ~1 nm have been synthesized.

The new bimetallic Au/CuO_x/SiO_2, Au/Pd/TiO_2, Au/Pt/TiO_2, and Au/RuO_2/θ-Al_2O_3 catalysts demonstrated a high efficiency in oxidation of alcohols to aldehydes or esters (Au/CuO_x/SiO_2, Au/Pd/TiO_2), and the oxidation of glycerol and propane-1,2-diol into lactic acid (Au/Pd/TiO_2, Au/Pt/TiO_2), as well as glycerol hydrodehydroxylation (Au/RuO_2/θ-Al_2O_3) (Figure 7).

The new materials allowed one to significantly enhance the activity/selectivity for the hydrogenation or partial oxidation of glycerol and other reactions (hydroamination, ring opening, and partial oxidation of various substrates). Glycerol (a by-product of biodiesel production) oxidation into lactic acid (desired high

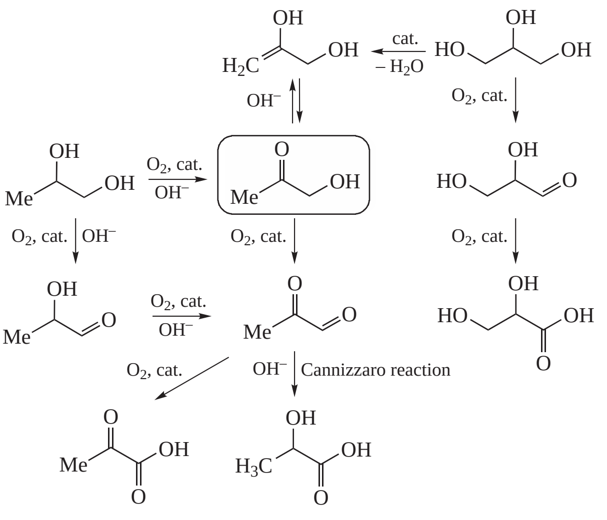


Figure 7 A proposed general pathway of lactic acid production from propane-1,2-diol and glycerol. The marked substance was obtained in the reaction mixture as an intermediate product.

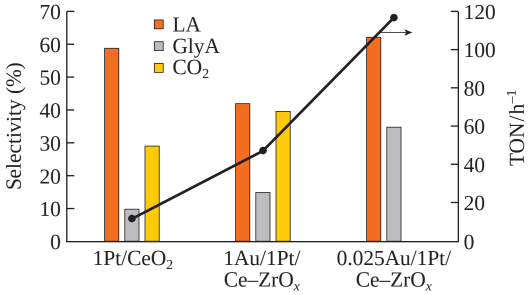


Figure 8 Activity of hybrid catalysts in the oxidation of glycerol into lactic acid [TON = mol(LA) mol(Au + Pt)$^{-1}$ h^{-1}; LA – lactic acid; GlyA – glyceric acid].

value added monomer for biodegradable packaging materials) occurs on bimetallic Au-Pt nanoparticles with enhanced selectivity and productivity (Figure 8). The rationale of the developed catalyst synthesis allows the loading of gold in the catalyst composition to be significantly reduced.[67,68]

The new catalytic system 1% Au/1% RuO_2/θ-Al_2O_3 for glycerol hydrodehydroxylation was much more active and selective compared to the monometallic Au/θ-Al_2O_3 and RuO_2/θ-Al_2O_3 samples.

Capturing molecular level dynamics in chemical reactions

Chemical reactions in solution are difficult to directly visualize using available methods. NMR spectroscopy and mass spectrometry provide valuable spectral information, which can be interpreted in terms of molecular structures and transformations. However, an overall mechanistic picture is often difficult to resolve. Electron microscopy gives an important strength into the mechanistic investigations that allows visualization of the objects being studied.

One of our goals was to develop an approach to capture molecular level dynamics in chemical transformations. The successful application of electron microscopy to capture system dynamics was demonstrated in a study of carbohydrates conversion to 5-(hydroxymethyl)furfural (5-HMF).[69] The key point was to use ionic liquids as a medium to carry out the chemical transformations. High stability under vacuum and suitable properties for microscopy observation made it possible to record a video stream that reflected the rearrangements that occurred in the studied system at micro-sized and nano-sized levels. It was found that the presence of a small amount of water induced a structured reaction medium and the formation of dynamic microreactors (Figure 9).[69(*a*)] The morphology of the microreactors correlated to the observed selectivity and yielded the carbohydrates conversion process.

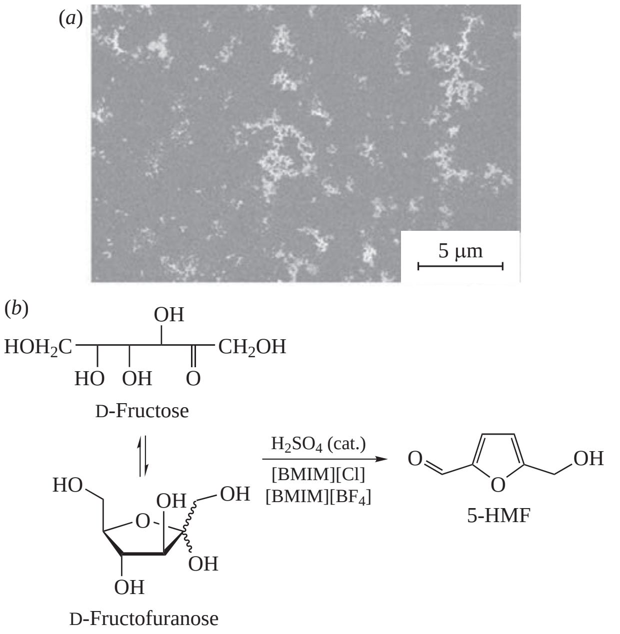


Figure 9 (*a*) Electron microscopy image of the reaction mixture and (*b*) catalytic transformation of fructose to 5-HMF. Figure from ref. 69(*a*). © 2016 Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

The study has shown that reaction dynamics can be directly captured by microscopy and visualized in video movies. Further development of this unique technique will be a fascinating direction for the present project, especially applying this methodology to the area of catalysis.[70]

3D printing and additive technologies in chemistry

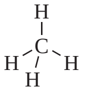
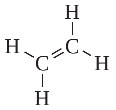
Modern organic chemistry and catalysis can build complex molecular systems that possess outstanding properties. However, in many cases it is difficult to fabricate a product for practical needs due to the high cost of the synthetic process, difficulties in isolation and purification, and necessity of handling toxic waste. A real advancement was recently made by implementing additive technologies for the design and construction of chemical reactors, labware and research equipment using 3D printing.[71] 3D printing provides a simple and convenient way to create customized chemical equipment. However, the potential of 3D printing is not limited to equipment.

As an example of synthetic efficiency, construction of a paramount variety of proteins and peptides in living organisms can be considered, which was achieved with a limited number of universal building blocks – amino acids [Figure 10(*a*)]. Reproduction and evolutionary development involves even smaller number of nucleotides, which embed genetic information into DNA and RNA [Figure 10(*b*)]. Advanced technological manufacturing has resulted in powerful additive technologies that are now routinely available in 3D printers [Figure 10(*c*)]. These three cases represent universal and powerful techniques for the construction of molecules and matter. The examples show that the cost-efficiency of a bottom-up approach can be combined with the absence of the waste of an additive process. If we anticipate the concept towards organic synthesis, we can project a kind of 3D printing of organic molecules [Figure 10(*d*)].

The process of molecular 3D printing would be efficient if a limited number of building blocks will be sufficient to assemble the desired products. A search for the universal building units for molecular 3D printing suggests alkynes as possible candidates (Table 2).[72] Comparing the three main classes of widely available hydrocarbon sources reveals the advantage of alkynes in terms of the number of activated substituents and waste-free atom-economic addition steps (Table 2).[72]

Of course, on the moment possible resolution of 3D printers is not high enough for additive manufacturing at the molecular

Table 2 Potential building units for molecular 3D printing.

Building unit	Number of less active substituents on each carbon atom	Number of activated substituents on each carbon atom	Number of possible atom-economic addition reactions
	4	0	0
	2	0	1
H−C≡C−H	0	1	2

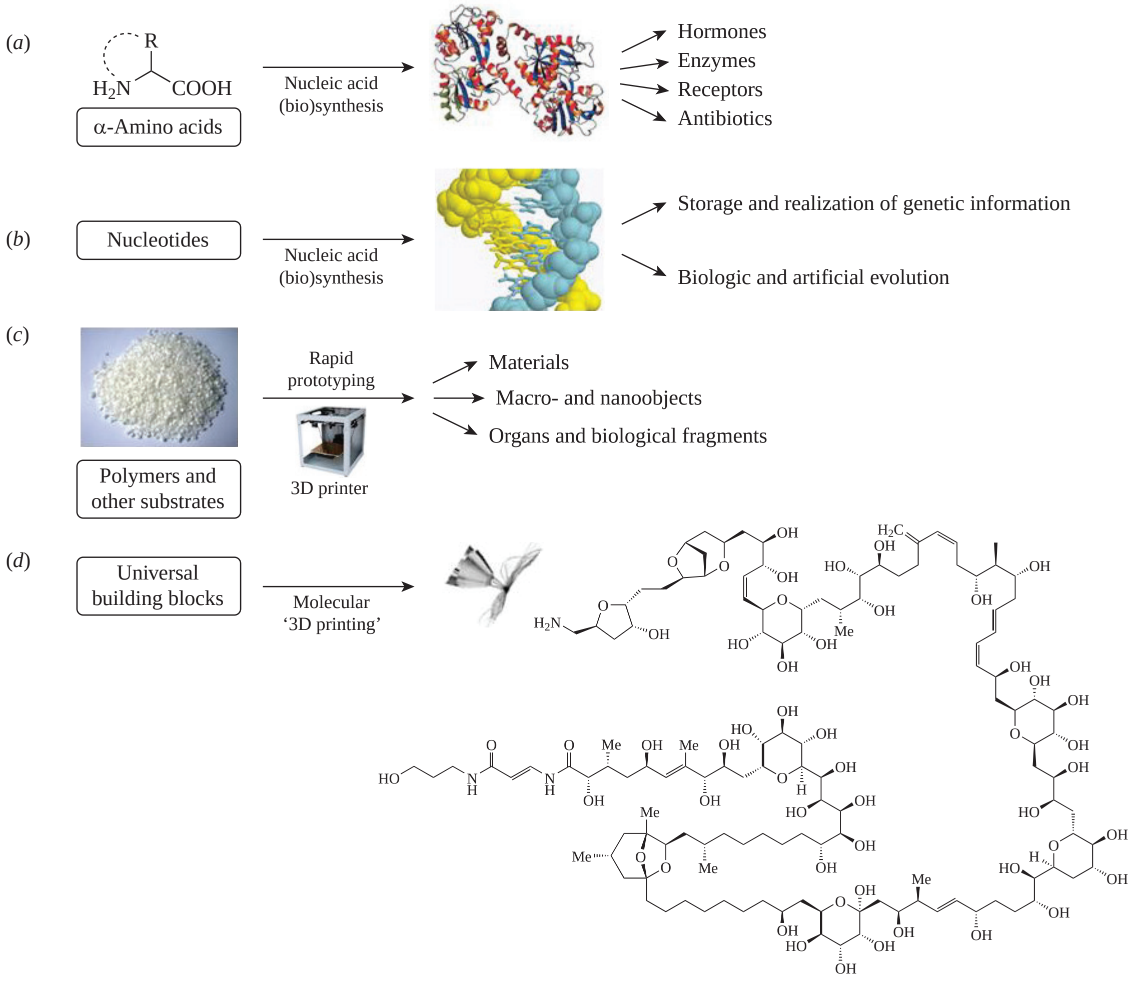


Figure 10 Efficient production of molecules and materials with universal building blocks.[72]

level. The smallest dimension of 1 μm over 200 nm was accessible by three-dimensional direct laser writing followed by pyrolysis.[73] To obtain molecular level 3D printing, resolution enhancement by about an order of magnitude may be required.

Conclusions

To summarize, we have investigated different research directions to develop the ongoing project on organic and hybrid molecular systems (the initiative described earlier[10]). Depending on the application and target, chemical systems range from small molecule to oligomeric, nanoscale and further to hybrid architectures and microscale frameworks (Figure 11). In order to build the desired level of molecular complexity, direct organic synthesis evolves to manual assembling of the building units, bottom-up self-assembling, and further to supramolecular arrangement and microscale aggregation. At the utmost right position of the figure (Figure 11) at the micrometer scale region, other type of bottom-up assembly – additive technologies and 3D printing – has already demonstrated promising potential. The aim of the present project is to make progress in the individual development of each of the synthetic methods, as well as to develop a unifying concept for the efficient construction of molecular complexity at various levels.

The development of efficient, energy-saving and environmentally safe synthetic methodologies for the regio-, stereo- and enantioselective formation of chemical bonds remains a crucial challenge in the area of small organic molecule synthesis. Among the state-of-art methodologies, atom-economy domino reactions, highly enantioselective organocatalytic transformations and 'clean' synthetic procedures that do not require usage of toxic reagents and solvents are obviously preferable. Important nitrogen-oxygen systems, natural compound analogues and useful bioactive molecules are attainable by means of these methodologies.

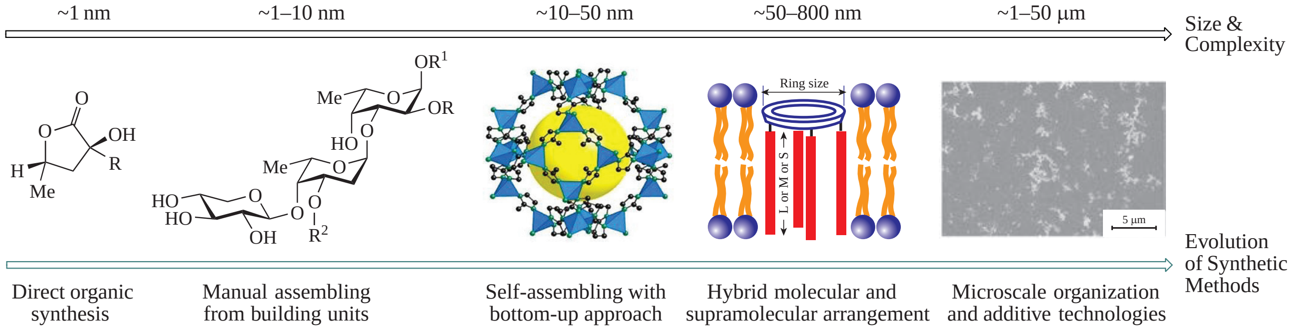


Figure 11 Evolution of synthetic methods facilitated by increasing size and complexity of chemical systems.

The key challenges for the bioorganic and hybrid system fields remained connected to the development of efficient stereo- and regiospecific syntheses of target bioorganic ligands in the functional form, which permits further conjugation with carriers and labels. The driving forces of these studies were determined by the need for fundamental biological or applied biomedical investigations. With the recent progress in this field and particularly with the development of the enzymatic synthesis of natural ligands, main attention tends to shift to the design and investigation of the 3D spatial organization of bioorganic and hybrid systems to manage the efficiency of their biological recognition by purified or non-purified receptors in the artificial or natural environments.

The further challenges in heterogeneous systems are related to the improvement and optimization of supported and mixed matrix membranes to separate important gas mixtures due to the synthesis of new MOF structures and better preparation recipes. The core-shell metal nanoparticles are interesting for the application in a number of catalytic processes involving diverse substrates and transformations: hydrogenation, partial oxidation, dehydrogenation (hydrogen storage), isomerization, intra- and intermolecular hydroamination, Fischer–Tropsch synthesis, and ring opening of cyclic hydrocarbons.

Nearest challenges in the mechanistic studies include direct visualization of chemical processes at the molecular level using spectral (NMR and MS), microscopic (SEM and TEM) and computational techniques. Revealing the basic principles that govern, build and change the molecular complexity will extend the possibilities for additive technologies to a fascinating level of direct 3D printing of molecules.

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References

1 G. M. Whitesides, *Angew. Chem. Int. Ed*., 2015, **54**, 3196.

2 (*a*) A. McNally, C. K. Prier and D. W. C. MacMillan, *Science*, 2011, **334**, 1114; (*b*) K. D. Collins, T. Gensch and F. Glorius, *Nat. Chem*., 2014, **6**, 859.

3 (*a*) A. P. Alivisatos, A. M. Andrews, E. S. Boyden, M. Chun, G. M. Church, K. Deisseroth, J. P. Donoghue, S. E. Fraser, J. Lippincott-Schwartz, L. L. Looger, S. Masmanidis, P. L. McEuen, A. V. Nurmikko, H. Park, D. S. Peterka, C. Reid, M. L. Roukes, A. Scherer, M. Schnitzer, T. J. Sejnowski, K. L. Shepard, D. Tsao, G. Turrigiano, P. S. Weiss, C. Xu, R. Yuste and X. Zhuang, *ACS Nano*, 2013, **7**, 1850; (*b*) A. P. Alivisatos, M. Chun, G. M. Church, K. Deisseroth, J. P. Donoghue, R. J. Greenspan, P. L. McEuen, M. L. Roukes, T. J. Sejnowski, P. S. Weiss and R. Yuste, *Science*, 2013, **339**, 1284; (*c*) J. Wang, L. Ren, L. Li, W. Liu, J. Zhou, W. Yu, D. Tong and S. Chen, *Lab Chip*, 2009, **9**, 644; (*d*) A. Zhang and C. M. Lieber, *Chem. Rev*., 2016, **116**, 215.

4 (*a*) L. Ma, J. Kim, R. Hatzenpichler, M. A. Karymov, N. Hubert, I. M. Hanan, E. B. Chang and R. F. Ismagilov, *Proc. Natl. Acad. Sci. USA*, 2014, **111**, 9768; (*b*) J. M. Yano, K. Yu, G. P. Donaldson, G. G. Shastri, P. Ann, L. Ma, C. R. Nagler, R. F. Ismagilov, S. K. Mazmanian and E. Y. Hsiao, *Cell*, 2015, **161**, 264.

5 M. P. Egorov, *Russ. Chem. Rev.*, 2014, **83**, E01.

6 V. P. Ananikov, L. L. Khemchyan, Yu. V. Ivanova, V. I. Bukhtiyarov, A. M. Sorokin, I. P. Prosvirin, S. Z. Vatsadze, A. V. Medved'ko, V. N. Nuriev, A. D. Dilman, V. V. Levin, I. V. Koptyug, K. V. Kovtunov, V. V. Zhivonitko, V. A. Likholobov, A. V. Romanenko, P. A. Simonov, V. G. Nenajdenko, O. I. Shmatova, V. M. Muzalevskiy, M. S. Nechaev, A. F. Asachenko, O. S. Morozov, P. B. Dzhevakov, S. N. Osipov, D. V. Vorobyeva, M. A. Topchiy, M. A. Zotova, S. A. Ponomarenko, O. V. Borshchev, Y. N. Luponosov, A. A. Rempel, A. A. Valeeva, A. Yu. Stakheev, O. V. Turova, I. S. Mashkovsky, S. V. Sysolyatin, V. V. Malykhin, G. A. Bukhtiyarova, A. O. Terent'ev and I. B. Krylov, *Russ. Chem. Rev*., 2014, **83**, 885.

7 V. P. Ananikov, X. Liu and U. Schneider, *Chem. Asian J*., 2016, **11**, 328.

8 D. S. Su, B. Zhang and R. Schlögl, *Chem. Rev.*, 2015, **115**, 2818.

9 (*a*) S. S. Zalesskiy, E. Danieli, B. Blümich and V. P. Ananikov, *Chem. Rev.*, 2014, **114**, 5641; (*b*) V. V. Kachala, L. L. Khemchyan, A. S. Kashin, N. V. Orlov, A. A. Grachev, S. S. Zalesskiy and V. P. Ananikov, *Russ. Chem. Rev.*, 2013, **82**, 648.

10 V. P. Ananikov, E. A. Khokhlova, M. P. Egorov, A. M. Sakharov, S. G. Zlotin, A. V. Kucherov, L. M. Kustov, M. L. Gening and N. E. Nifantiev, *Mendeleev Commun.*, 2015, **25**, 75.

11 (*a*) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998; (*b*) *Handbook of Green Chemistry and Technology*, eds. J. H. Clark and D. Macquarrie, Blackwell Science Ltd., Oxford, UK, 2002; (*c*) R. A. Sheldon, *Chem. Soc. Rev*., 2012, **41**, 1437.

12 A. M. Churakov and V. A. Tartakovsky, *Chem. Rev.*, 2004, **104**, 2601.

13 (*a*) K. O. Christe, D. A. Dixon, M. Vasiliu, R. I. Wagner, R. Haiges, J. A. Boatz and H. L. Ammon, *Propellants Explos. Pyrotech*., 2015, **40**, 463; (*b*) K. R. Jorgensen, G. A. Oyedepo and A. K. Wilson, *J. Hazard. Mater*., 2011, **186**, 583; (*c*) P. Politzer, P. Lane and J. S. Murray, *Cent. Eur. J. Energ. Mater*., 2013, **10**, 37.

14 J. A. Hrabie and L. K. Keefer, *Chem. Rev.*, 2002, **102**, 1135.

15 O. Yu. Smirnov, A. M. Churakov, A. Yu. Tyurin, Yu. A. Strelenko, S. L. Ioffe and V. A. Tartakovsky, *Russ. Chem. Bull., Int. Ed*., 2002, **51**, 1849 (*Izv. Akad. Nauk, Ser. Khim.*, 2002, 1701).

16 M. S. Klenov, A. M. Churakov, Yu. A. Strelenko, I. V. Ananyev, K. A. Lyssenko and V. A. Tartakovsky, *Tetrahedron Lett*., 2015, **56**, 5437.

17 M. S. Klenov, O. V. Anikin, A. M. Churakov, Yu. A. Strelenko, I. V. Fedyanin, I. V. Ananyev and V. A. Tartakovsky, *Eur. J. Org. Chem*., 2015, 6170.

18 S. G. Zlotin, A. M. Churakov, O. A. Luk'yanov, N. N. Makhova, A. Yu. Sukhorukov and V. A. Tartakovsky, *Mendeleev Commun*., 2015, **25**, 399.

19 K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem. Int. Ed*., 2006, **45**, 7134.

20 (*a*) *Multicomponent Reactions*, eds. J. Zhu and H. Bienayme, Wiley-VCH, Weinheim, 2005; (*b*) *Synthesis of Heterocycles via Multicomponent Reactions I*, eds. R. V. A. Orru and E. Ruijter, Springer, New York, 2010.

21 A. N. Vereshchagin, M. N. Elinson, Yu. E. Anisina, F. V. Ryzhkov, A. S. Goloveshkin, I. S. Bushmarinov, S. G. Zlotin and M. P. Egorov, *Mendeleev Commun*., 2015, **25**, 424.

22 D. R. Anderson, S. Hegde, E. Reinhard, L. Gomez, W. F. Vernier, L. Lee, S. Liu, A. Sambandam, P. A. Snider and L. Masih, *Bioorg. Med. Chem. Lett*., 2005, **15**, 1587.

23 (*a*) *Science of Synthesis: Asymmetric Organocatalysis*, eds. B. List and K. Maruoka, Thieme, Stuttgart, 2012, vols. 1, 2; (*b*) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, ed. P. I. Dalco, Wiley-VCH, Weinheim, 2013, vols. 1–3; (*c*) U. Scheffler and R. Mahrwald, *Chem. Eur. J*., 2013, **19**, 14346.

24 A. S. Kucherenko, D. E. Siyutkin, O. V. Maltsev, S. V. Kochetkov and S. G. Zlotin, *Russ. Chem. Bull., Int. Ed*., 2012, **61**, 1313 (*Izv. Akad. Nauk, Ser. Khim.*, 2012, 1299).

25 V. G. Lisnyak, A. S. Kucherenko, E. F. Valeev and S. G. Zlotin, *J. Org. Chem*., 2015, **80**, 9570.

26 (*a*) O. Tokuda, T. Kano, W. G. Gao, I. Ikemoto and K. Maruoka, *Org. Lett.*, 2005, **7**, 5103; (*b*) Z. Duan, J. Han, P. Qian, Z. Zhang, Y. Wang and Y. Pan, *Beilstein J. Org. Chem.*, 2014, **10**, 969.

27 S. G. Zlotin and S. V. Kochetkov, *Russ. Chem. Rev*., 2015, **84**, 1077.

28 (*a*) H. Pellissier, *Adv. Synth. Catal*., 2012, **354**, 237; (*b*) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne and J. Rodriguez, *Synthesis*, 2013, **45**, 1909; (*c*) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev*., 2014, **114**, 2390; (*d*) P. Chauhan, S. Mahajan, U. Kaya, D. Hack and D. Enders, *Adv. Synth. Catal*., 2015, **357**, 253.

29 F. M. Kerton, *Alternative Solvents for Green Chemistry*, RSC Publishing, Cambridge, 2010.

30 (*a*) W. Leitner, in *Handbook of Green Chemistry*, eds. W. Leitner and P. G. Jessop, Wiley-VCH, Weinheim, 2010, vol. 4, p. 1412; (*b*) P. G. Jessop, *J. Supercrit. Fluids*, 2006, **38**, 211; (*c*) S. Liu and J. Xiao, *J. Mol. Catal. A: Chem*., 2007, **270**, 1.

31 (*a*) A. G. Nigmatov, I. V. Kuchurov, D. E. Siyutkin and S. G. Zlotin, *Tetrahedron Lett*., 2012, **53**, 3502; (*b*) I. V. Kuchurov, A. G. Nigmatov, E. V. Kryuchkova, A. A. Kostenko, A. S. Kucherenko and S. G. Zlotin, *Green Chem*., 2014, **16**, 1521.

32 E. V. Filatova, O. V. Turova, I. V. Kuchurov, A. A. Kostenko, A. G. Nigmatov and S. G. Zlotin, *J. Supercrit. Fluids*, 2016, **109**, 35.

33 (*a*) I. Jacquemond-Collet, F. Benoit-Vical, M. Valentin, A. Stanislas, E. Malli and M. Fourasté, *Planta Med*., 2002, **68**, 68; (*b*) I. Jacquemond-Collet, S. Hannedouche, N. Fabre and I. Fourast, *Phytochemistry*, 1999, **51**, 1167.

34 K. M. Witherup, R. W. Ransom, A. C. Graham, A. M. Bernard, M. J. Salvatore, W. C. Lumma, P. S. Anderson, S. M. Pitzenberger and S. L. Varga, *J. Am. Chem. Soc.*, 1995, **117**, 6682.

35 P. A. Clarke, S. Santosa and W. H. C. Martin, *Green Chem*., 2007, **9**, 438.

36 (*a*) J. Alemán and S. Cabrera, *Chem. Soc. Rev*., 2013, **42**, 774; (*b*) M. E. Abbasov and D. Romo, *Nat. Prod. Rep*., 2014, **31**, 1318.

37 B. Ernst and J. L. Magnani, *Nat. Rev. Drug Discov*., 2009, **8**, 661.

38 A. Fernández-Tejada, F. J. Cañada and J. Jiménez-Barbero, *Chem. Eur. J*., 2015, **21**, 10616.

39 A. Fernández-Tejada, F. J. Cañada and J. Jiménez-Barbero, *ChemMedChem*, 2015, **10**, 1291.

40 N. Ustyuzhanina, B. Komarova, N. Zlotina, V. Krylov, A. Gerbst, Y. Tsvetkov and N. Nifantiev, *Synlett.*, 2006, 921.

41 B. S. Komarova, Y. E. Tsvetkov and N. E. Nifantiev, *Chem. Rec*., 2016, **16**, 488.

42 B. S. Komarova, M. V. Orekhova, Y. E. Tsvetkov and N. E. Nifantiev, in *Specialist Periodical Reports: Carbohydrate Chemistry – Chemical and Biological Approaches*, eds. A. P. Rauter, T. Lindhorst and Y. Queneau, The Royal Society of Chemistry, 2016, vol. 41, p. 187.

43 B. S. Komarova, M. V. Orekhova, Y. E. Tsvetkov, R. Beau, V. Aimanianda, J.-P. Latgé and N. E. Nifantiev, *Chem. Eur. J*., 2015, **21**, 1029.

44 A. A. Karelin, Y. E. Tsvetkov, E. Paulovičová, L. Paulovičová and N. E. Nifantiev, *Eur. J. Org. Chem.*, 2016, 1173.

45 (*a*) Y. V. Mironov, A. A. Sherman and N. E. Nifantiev, *Tetrahedron Lett.*, 2004, **45**, 9107; (*b*) E. A. Khatuntseva, A. A. Sherman, Y. E. Tsvetkov and N. E. Nifantiev, *Tetrahedron Lett*., 2015, **57**, 708.

46 L. K. Shubina, T. N. Makarieva, D. V. Yashunsky, N. E. Nifantiev, V. A. Denisenko, P. S. Dmitrenok, S. A. Dyshlovoy, S. N. Fedorov, V. B. Krasokhin, S. H. Jeong, J. Han and V. A. Stonik, *J. Nat. Prod*., 2015, **78**, 1383.

47 D. V. Yashunsky, E. V. Kulakovskaya, T. V. Kulakovskaya, O. S. Zhukova, M. V. Kiselevskiy and N. E. Nifantiev, *J. Carbohydr. Chem.*, 2016, **34**, 460.

48 Z. Song and X. Xu, *J. Cancer Res. Ther*., 2014, **10**, 3.

49 M. L. Gening, Y. E. Tsvetkov, G. B. Pier and N. E. Nifantiev, *Carbohydr. Res*., 2007, **342**, 567.

50 M. L. Gening, D. V. Titov, A. A. Grachev, A. G. Gerbst, O. N. Yudina, A. S. Shashkov, A. O. Chizhov, Y. E. Tsvetkov and N. E. Nifantiev, *Eur. J. Org. Chem.*, 2010, **13**, 2465.

51 M. L. Gening, D. V. Titov, S. Cecioni, A. Audfray, A. G. Gerbst, Y. E. Tsvetkov, V. B. Krylov, A. Imberty, N. E. Nifantiev and S. Vidal, *Chem. Eur. J*., 2013, **19**, 9272.

52 T. Saha, A. Roy, M. L. Gening, D. V. Titov, A. G. Gerbst, Y. E. Tsvetkov, N. E. Nifantiev and P. Talukdar, *Chem. Commun.*, 2014, **50**, 5514.

53 A. Roy, T. Saha, M. L. Gening, D. V. Titov, A. G. Gerbst, Y. E. Tsvetkov, N. E. Nifantiev and P. Talukdar, *Chem. Eur. J*., 2015, **21**, 17445.

54 T. Saha, S. Dasari, D. Tewari, A. Prathap, K. M. Sureshan, A. K. Bera, A. Mukherjee and P. Talukdar, *J. Am. Chem. Soc.*, 2014, **136**, 14128.

55 N. E. Ustyuzhanina, M. I. Bilan, A. G. Gerbst, N. A. Ushakova, E. A. Tsvetkova, A. S. Dmitrenok, A. I. Usov and N. E. Nifantiev, *Carbohydr. Polym*., 2016, **136**, 826.

56 N. E. Ustyuzhanina, M. I. Bilan, N. A. Ushakova, A. I. Usov, M. V. Kiselevskiy and N. E. Nifantiev, *Glycobiology*, 2014, **24**, 1265.

57 M. Suzuki, L. Bachelet-Violette, F. Rouzet, A. Beilvert, G. Autret, M. Maire, C. Menager, L. Louedec, C. Choqueux, P. Saboural, O. Haddad, C. Chauvierre, F. Chaubet, J.-B. Michel, J.-M. Serfaty and D. Letourneur, *Nanomedicine (Lond.)*, 2014, **10**, 73.

58 T. Bonnard, J.-M. Serfaty, C. Journé, B. Ho Tin Noe, D. Arnaud, L. Louedec, M. Derkaoui, D. Letourneur, C. Chauvierre, C. Le Visage, *Acta Biomater*., 2014, **10**, 3535.

59 M. Juenet, M. Varna, R. Aid-Launais, C. Chauvierre and D. Letourneur, *Biochem. Biophys. Res. Commun*., 2015, **468**, 476.

60 O. M. Yaghi, G. Li and H. Li, *Nature*, 1995, **378**, 703.

61 A. U. Czaja, N. Trukhan and U. Müller, *Chem. Soc. Rev*., 2009, **38**, 1284.

62 G. Férey, C. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surblé and I. Margiolaki, *Science*, 2005, **309**, 2040.

63 P. Mélinon, S. Begin-Colin, J. L. Duvail, F. Gauffre, N. H. Boime, G. Ledoux, J. Plain, P. Reiss, F. Silly and B. Warot-Fonrose, *Phys. Rep*., 2014, **543**, 163.

64 R. Kaur, A. Hasan, N. Iqbal, S. Alam, M. K. Saini and S. K. Raza, *J. Sep. Sci.*, 2014, **37**, 1805.

65 J.-H. Lin and V. V. Guliants, *Appl. Catal. A: General*, 2012, **445–446**, 187.

66 (*a*) V. I. Isaeva, A. L Tarasov, V. V. Chernyshev and L. M. Kustov, *Mendeleev Commun.*, 2015, **25**, 466; (*b*) S. S. Chiu, S. M. Lo, J. P. Charmant, A. G. Orpen and I. D. Williams, *Science*, 1999, **283**, 1148; (*c*) K. S. Park, Z. Ni, A. P. Côté, J. Y. Choi, R. Huang, F. J. Uribe-Romo, H. K. Chae, M. O'Keeffe and O. M. Yaghi, *Proc. Natl. Acad. Sci. USA*, 2006, **103**, 10186; (*d*) V. I. Isaeva, M. I. Barkova, L. M. Kustov, D. A. Syrtsova, E. A. Efimova and V. V. Teplyakov, *J. Mater. Chem. A*, 2015, **3**, 7469.

67 E. A. Redina, O. A. Kirichenko, A. A. Greish, A. V. Kucherov, O. P. Tkachenko, G. I. Kapustin, I. V. Mishin and L. M. Kustov, *Catal. Today*, 2015, **246**, 216.

68 E. Redina, A. Greish, R. Novikov, A. Strelkova, O. Kirichenko, O. Tkachenko, G. Kapustin, I. Sinev and L. Kustov, *Appl. Catal. A: General*, 2015, **491**, 170.

69 (*a*) A. S. Kashin, K. I. Galkin, E. A. Khokhlova and V. P. Ananikov, *Angew. Chem. Int. Ed*., 2016, **55**, 2161; (*b*) E. A. Khokhlova, V. V. Kachala and V. P. Ananikov, *ChemSusChem*, 2012, **5**, 783; (*c*) K. I. Galkin, E. A. Krivodaeva, L. V. Romashov, S. S. Zalesskiy, V. V. Kachala, J. V. Burykina and V. P. Ananikov, *Angew. Chem. Int. Ed*., 2016, **55**, 8338.

70 (*a*) E. O. Pentsak, A. S. Kashin, M. V. Polynski, K. O. Kvashnina, P. Glatzel and V. P. Ananikov, *Chem. Sci*., 2015, **6**, 3302; (*b*) V. P. Ananikov, *ACS Catal.*, 2015, **5**, 1964; (*c*) E. S. Degtyareva, J. V. Burykina, A. N. Fakhrutdinov, E. G. Gordeev, V. N. Khrustalev and V. P. Ananikov, *ACS Catal*., 2015, **5**, 7208; (*d*) E. O. Pentsak, E. G. Gordeev and V. P. Ananikov, *ACS Catal*., 2014, **4**, 3806.

71 (a) M. D. Symes, P. J. Kitson, J. Yan, C. J. Richmond, G. J. T. Cooper, R. W. Bowman, T. Vilbrandt and L. Cronin, *Nat. Chem.*, 2012, **4**, 349; (*b*) P. J. Kitson, R. J. Marshall, D. Long, R. S. Forgan and L. Cronin, *Angew. Chem. Int. Ed.*, 2014, **53**, 12723.

72 K. I. Galkin and V. P. Ananikov, *Russ. Chem. Rev*., 2016, **85**, 226.

73 J. Bauer, A. Schroer, R. Schwaiger and O. Kraft, *Nat. Mater.*, 2016, ASAP, doi:10.1038/nmat4561.

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