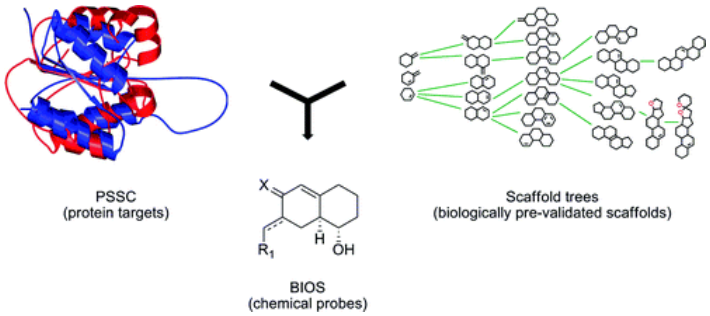
- Bioactivity-Guided Navigation of Chemical Space
  Bon, R. S.; Waldmann, H. *Acc. Chem. Res.* **2010**, *43*, 1103–1114.
  Abstract:



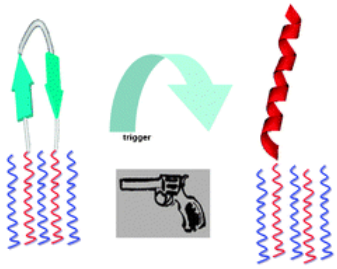
A central aim of biological research is to elucidate the many roles of proteins in complex, dynamic living systems; the selective perturbation of protein function is an important tool in achieving this goal. Because chemical perturbations offer opportunities often not accessible with genetic methods, the development of small-molecule modulators of protein function is at the heart of chemical biology research. In this endeavor, the identification of biologically relevant starting points within the vast chemical space available for the design of compound collections is a particularly relevant, yet difficult, task. In this Account, we present our research aimed at linking chemical and biological space to define suitable starting points that guide the synthesis of compound collections with biological relevance.

Both protein folds and natural product (NP) scaffolds are highly conserved in nature. Whereas different amino acid sequences can make up ligand-binding sites in proteins with highly similar fold types, differently substituted NPs characterized by particular scaffold classes often display diverse biological activities. Therefore, we hypothesized that (i) ligand-binding sites with similar ligand-sensing cores embedded in their folds would bind NPs with similar scaffolds and (ii) selectivity is ensured by variation of both amino acid side chains and NP substituents. To investigate this notion in compound library design, we developed an approach termed biology-oriented synthesis (BIOS). BIOS employs chem- and bioinformatic methods for mapping biologically relevant chemical space and protein space to generate hypotheses for compound collection design and synthesis. BIOS also provides hypotheses for potential bioactivity of compound library members. On the one hand, protein structure similarity clustering (PSSC) is used to identify ligand binding sites with high subfold similarity, that is, high structural similarity in their ligand-sensing cores. On the other hand, structural classification by scaffold trees (for example, structural classification of natural products or SCONP), when combined with software tools like “Scaffold Hunter”, enables the hierarchical structural classification of small-molecule collections in tree-like arrangements, their annotation with bioactivity data, and the intuitive navigation of chemical space. Brachiation (in a manner analogous to tree-swinging primates) within the scaffold trees serves to identify new starting points for the design and synthesis of small-molecule libraries, and PSSC may be used to select potential protein targets.

The introduction of chemical diversity in compound collections designed according to the logic of BIOS is essential for the frequent identification of small molecules with diverse biological activities. The continuing development of synthetic methodology, both on solid phase and in solution, enables the generation of focused small-molecule collections with sufficient substituent, stereochemical, and scaffold diversity to yield comparatively high hit rates in biochemical and biological screens from

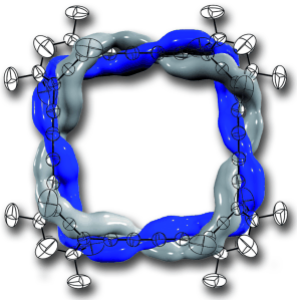
relatively small libraries. BIOS has also allowed the identification of new ligand classes for several different proteins and chemical probes for the study of protein function in cells.

- Stimulus responsive peptide based materials
  Löwik, D. W. P. M.; Leunissen, E. H. P.; van den Heuvel, M.; Hansen, M. B.; van Hest, J. C. M. *Chem. Soc. Rev.* **2010**, *39*, 3394-3412.
  Abstract:



In this *tutorial review* we give an introduction into the field of stimulus responsive peptide based materials illustrated by some recent and current developments. We have tried to categorize them according to the stimulus the materials are responsive to, being pH, temperature, metal ions, enzymes and light. Because we have focused on the structural changes that these stimuli effect we have further classified the topics according to the secondary structures that are involved. These changes in molecular structure in turn cause a change in the macroscopic properties of the material they constitute. It is believed that these materials, often referred to as smart materials, have a great potential being applicable in areas like drug delivery, tissue engineering and bio-sensors.

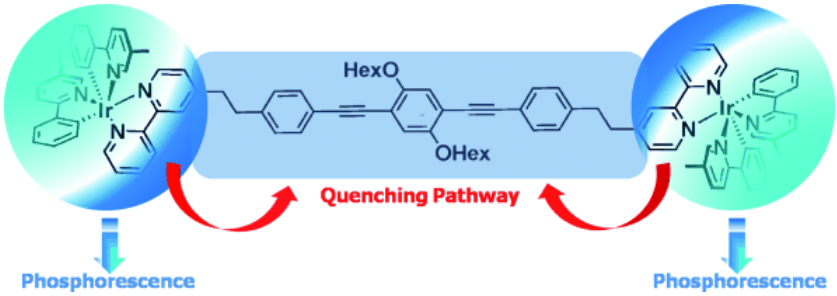
- Enantiomerically Pure Alleno–Acetylenic Macrocycles: Synthesis, Solid-State Structures, Chiroptical Properties, and Electron Localization Function Analysis
  Rivera-Fuentes, P.; Alonso-Gómez, J. L.; Petrovic, A.; Seiler, P.; Santoro, F.; Harada, N.; Berova, N.; Rzepa, H.; Diederich, F. *Chem. Eur. J.* **2010**, *16*, 9796–9807.
  Abstract:



New enantiomerically pure alleno–acetylenic macrocycles were prepared by oxidative homocoupling of optically active 1,3-diethynylallenes. Enantiomer separation resulted from a combined strategy of synthesis and chiral HPLC techniques. Two other achiral stereoisomers were also isolated and fully characterized. In addition, the X-ray structures of the chiral D_4- and C_2-symmetric macrocycles are reported. The chiroptical properties of these macrocycles are discussed on the basis of quantum chemical calculations, by using the CAM-B3LYP functional. Studies were carried out to investigate the vibronic fine structure observed experimentally in the UV/Vis and CD spectra. The origin of the intense chiroptical response of the chiral alleno–acetylenic macrocycles is explained by considering the topology of the molecular orbitals involved, thus relating electronic properties to structural

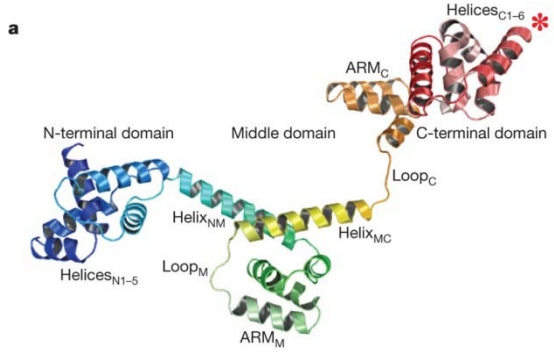
features. Further analysis of the canonical molecular orbitals and the electron localization function (ELF) shows that these macrocycles belong to a relatively rare class of highly stable and formally anti-aromatic Hückel compounds.

- Dumbbell-Shaped Dinuclear Iridium Complexes and Their Application to Light-Emitting Electrochemical Cells
  Costa, R.; Fernández, G.; Sánchez, L.; Martín, N.; Ortí, E.; Bolink, H. *Chem. Eur. J.* **2010**, *16*, 9855–9863.
  Abstract:



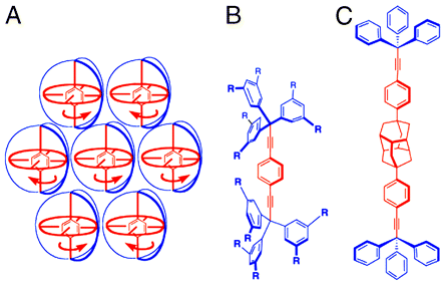
A novel family of dumbbell-shaped dinuclear complexes in which an oligophenyleneethynylene spacer is linked to two heteroleptic iridium(III) complexes is presented. The synthesis, as well as the electrochemical and photophysical characterization of the new complexes, is reported. The experimental results are interpreted with the help of density functional theory calculations. From these studies we conclude that the lowest triplet excited state corresponds to a $^3\pi$–π^* state located on the conjugated spacer. The presence of this state below the ^{3}MLCT/^{3}LLCT emitting states of the end-capping Ir^{III} complexes explains the low quantum yields observed for the dinuclear complexes (one order-of-magnitude less) with respect to the mononuclear complexes. The potential application of the novel dinuclear complexes in optoelectronic devices has been tested by using them as the primary active component in double-layer light-emitting electrochemical cells (LECs). Although the luminance levels are low, the external quantum efficiency suggests that a near-quantitative internal electron-to-photon conversion occurs in the device. This indicates that the emission inside the device is highly optimized and that the self-quenching associated with the high concentration of the complex in the active layer is minimized.

- Structure of the torque ring of the flagellar motor and the molecular basis for rotational switching
  Lee, L. K.; Ginsburg, M. A.; Crovace, C.; Donohoe, M.; Stock, D. *Nature* **2010**, *466*, 996–1000.
  Abstract:



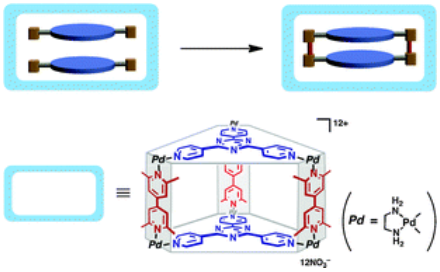
The flagellar motor drives the rotation of flagellar filaments at hundreds of revolutions per second, efficiently propelling bacteria through viscous media. The motor uses the potential energy from an electrochemical gradient of cations across the cytoplasmic membrane to generate torque. A rapid switch from anticlockwise to clockwise rotation determines whether a bacterium runs smoothly forward or tumbles to change its trajectory. A protein called FliG forms a ring in the rotor of the flagellar motor that is involved in the generation of torque through an interaction with the cation-channel-forming stator subunit MotA. FliG has been suggested to adopt distinct conformations that induce switching but these structural changes and the molecular mechanism of switching are unknown. Here we report the molecular structure of the full-length FliG protein, identify conformational changes that are involved in rotational switching and uncover the structural basis for the formation of the FliG torque ring. This allows us to propose a model of the complete ring and switching mechanism in which conformational changes in FliG reverse the electrostatic charges involved in torque generation.

- Symmetry and dynamics of molecular rotors in amphidynamic molecular crystals
  Karlen, S. D.; Reyes, H.; Taylor, R. E.; Khan, S. I.; Hawthorne, M. F.; Garcia-Garibay, M. A. *Proc. Nat. Acad. Sci. USA* **2010**, *107*, 14973-14977.
  Abstract:



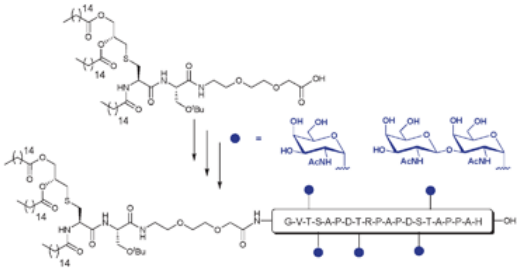
Rotary biomolecular machines rely on highly symmetric supramolecular structures with rotating units that operate within a densely packed frame of reference, stator, embedded within relatively rigid membranes. The most notable examples are the enzyme FoF1 ATP synthase and the bacterial flagellum, which undergo rotation in steps determined by the symmetries of their rotators and rotating units. Speculating that a precise control of rotational dynamics in rigid environments will be essential for the development of artificial molecular machines, we analyzed the relation between rotational symmetry order and equilibrium rotational dynamics in a set of crystalline molecular gyroscopes with rotators having axial symmetry that ranges from two- to fivefold. The site exchange frequency for these molecules in their closely related crystals at ambient temperature varies by several orders of magnitude, up to *ca.* 4.46×10^8 s^{-1}.

- Self-assembled cage as an *endo*-template for cyclophane synthesis
  Yamauchi, Y.; Fujita, M. *Chem. Commun.* **2010**, *46*, 5897-5899.
  Abstract:



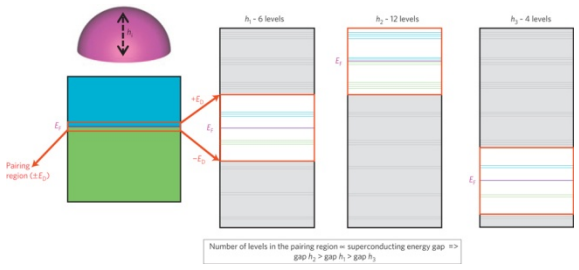
An organic-pillared coordination cage templated the quantitative formation of siloxane-bridged cyclophanes within its cavity via hydrolysis and condensation of 1,6- and 1,8-bis(trimethoxysilyl)pyrene.

- Synthesis of MUC1–lipopeptide chimeras
  Wilkinson, B. L.; Malins, L. R.; Chun, C. K. Y.; Payne, R. J. *Chem. Commun.* **2010**, *46*, 6249-6251.
  Abstract:



An efficient method for the convergent assembly of MUC1–lipopeptide vaccine candidates is described. Chimeras consisting of MUC1 glycopeptides (bearing multiple copies of the T_N and T tumour-associated carbohydrate antigens) tethered to the lipopeptide immunoadjuvant $Pam_3CysSer$ were synthesised in high yields using a fragment-based condensation strategy.

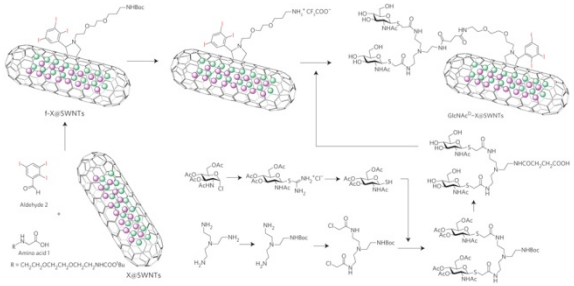
- Observation of shell effects in superconducting nanoparticles of Sn
  Bose, S.; García-García, A. M.; Ugeda, M. M.; Urbina, J. D.; Michaelis, C. H.; Brihuega, I.; Kern, K. *Nature Materials* **2010**, *9*, 550-554.
  Abstract:



In a zero-dimensional superconductor, quantum size effects (QSE) not only set the limit to superconductivity, but are also at the heart of new phenomena such as shell effects, which have been predicted to result in large enhancements of the superconducting energy gap. Here, we experimentally demonstrate these QSE through measurements on single, isolated Pb and Sn nanoparticles. In both systems superconductivity is ultimately quenched at sizes governed by the dominance of the quantum fluctuations of the order parameter. However, before the destruction of superconductivity, in Sn nanoparticles we observe giant oscillations in the superconducting energy gap with particle size leading to enhancements as large as 60%. These oscillations are the first

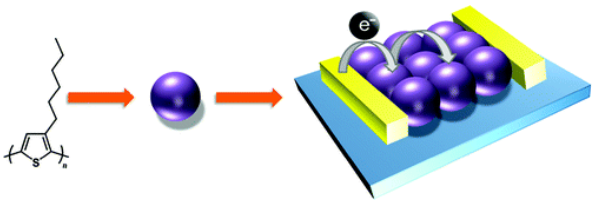
experimental proof of coherent shell effects in nanoscale superconductors. Contrarily, we observe no such oscillations in the gap for Pb nanoparticles, which is ascribed to the suppression of shell effects for shorter coherence lengths. Our study paves the way to exploit QSE in boosting superconductivity in low-dimensional systems.

- Filled and glycosylated carbon nanotubes for in vivo radioemitter localization and imaging
  Hong, S. Y.; Tobias, G.; Al-Jamal, K. T.; Ballesteros, B.; Ali-Boucetta, H.; Lozano-Perez, S.; Nellist, P. D.; Sim, R. B.; Finucane, C.; Mather, S. J.; Green, M. L. H.; Kostarelos, K.; Davis, B. D. *Nature Materials* **2010**, *9*, 485-490.
  Abstract:



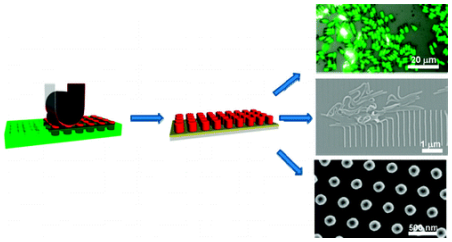
Functionalization of nanomaterials for precise biomedical function is an emerging trend in nanotechnology. Carbon nanotubes are attractive as multifunctional carrier systems because payload can be encapsulated in internal space whilst outer surfaces can be chemically modified. Yet, despite potential as drug delivery systems and radiotracers, such filled-and-functionalized carbon nanotubes have not been previously investigated in vivo. Here we report covalent functionalization of radionuclide-filled single-walled carbon nanotubes and their use as radioprobes. Metal halides, including Na125I, were sealed inside single-walled carbon nanotubes to create high-density radioemitting crystals and then surfaces of these filled–sealed nanotubes were covalently modified with biantennary carbohydrates, improving dispersibility and biocompatibility. Intravenous administration of Na125I-filled glyco-single-walled carbon nanotubes in mice was tracked in vivo using single-photon emission computed tomography. Specific tissue accumulation (here lung) coupled with high in vivo stability prevented leakage of radionuclide to high-affinity organs (thyroid/stomach) or excretion, and resulted in ultrasensitive imaging and delivery of unprecedented radiodose density. Nanoencapsulation of iodide within single-walled carbon nanotubes enabled its biodistribution to be completely redirected from tissue with innate affinity (thyroid) to lung. Surface functionalization of 125I-filled single-walled carbon nanotubes offers versatility towards modulation of biodistribution of these radioemitting crystals in a manner determined by the capsule that delivers them. We envisage that organ-specific therapeutics and diagnostics can be developed on the basis of the nanocapsule model described here.

- Synthesis, Properties, and Electronic Applications of Size-Controlled Poly(3-hexylthiophene) Nanoparticles
  Millstone, J. E.; Kavulak, D. J. F.; Woo, C. H.; Holcombe, T. W.; Westling, E. J.; Briseno, A. L.; Toney, M. F.; Fréchet, J. M. J. *Langmuir* **2010**, *26,* 13056–13061.
  Abstract:



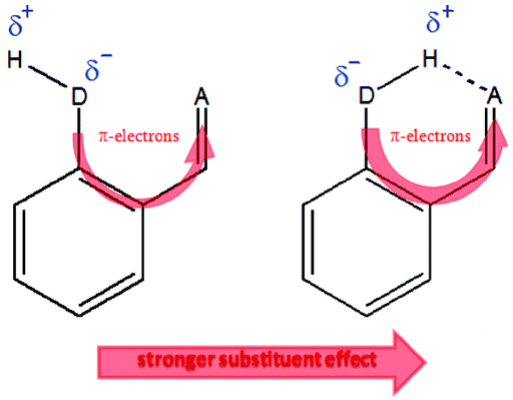
Semiconducting polymer nanoparticles have attracted increasing interest for the facile fabrication of organic electronic devices. These nanoparticles could provide the ability to control thin film morphology independently of optical and electronic properties. Using poly(3-hexylthiophene), we demonstrate surfactant-free synthesis and characterization of size-controlled, semicrystalline polymer nanoparticles. Our method produces discrete nanoparticles that can be deposited from solution into thin films. By controlling the molecular weight, polydispersity, and regioregularity of the polymer as well as varying its initial solution concentration, we tune both the size and crystallinity of the resulting nanoparticles. Organic field effect transistors (OFETs) using nanoparticles made from this method produce good semiconducting devices with hole mobilities on the order of 10^{-3} $cm^2/(V\ s)$. This approach to forming polymer nanoparticles is attractive for the introduction of solution-processable, well-characterized nanoscale crystalline domains of a variety of conjugated polymers and should be useful for the fabrication and optimization of organic electronic devices.

- Scalable, Shape-Specific, Top-Down Fabrication Methods for the Synthesis of Engineered Colloidal Particles
  Merkel, T. J.; Herlihy, K. P.; Nunes, J.; Orgel, R. M.; Rolland, J. P.; DeSimone, J. M. *Langmuir* **2010**, *26*, 13086-13096.
  Abstract:



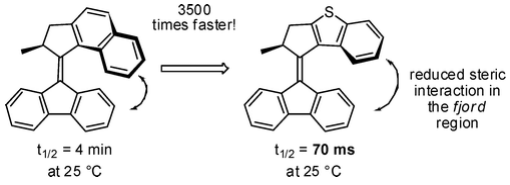
The search for a method to fabricate nonspherical colloidal particles from a variety of materials is of growing interest. As the commercialization of nanotechnology continues to expand, the ability to translate particle-fabrication methods from a laboratory to an industrial scale is of increasing significance. In this feature article, we examine several of the most readily scalable top-down methods for the fabrication of such shape-specific particles and compare their capabilities with respect to particle composition, size, shape, and complexity as well as the scalability of the method. We offer an extensive examination of particle replication in nonwetting templates (PRINT) with regard to the versatility and scalability of this technique. We also detail the specific methods used in PRINT particle fabrication, including harvesting, purification, and surface-modification techniques, with an examination of both past and current methods.

- H-Bonding-Assisted Substituent Effect
  Krygowski, T. M.; Zachara-Horeglad, J. E.; Palusiak, M. *J. Org. Chem.* **2010**, *75*, 4944–4949.
  Abstract:



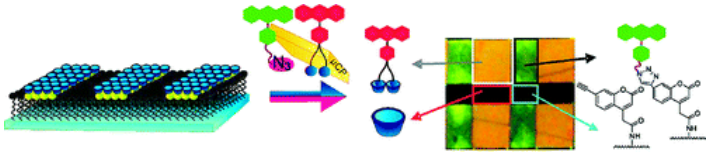
In this paper we investigate the influence of intramolecular noncovalent interaction, i.e., H-bonding and Li-bonding, on the properties of substituents communicating through the resonance (mesomeric) effect in such molecular systems as salicylaldehyde, *o*-hydroxy Schiff base, *o*-nitrosophenol, and their lithium analogues. The investigated systems are usually considered as molecular patterns of intramolecular resonance-assisted hydrogen bonds (or its analogues in the case of Li-bonded systems). We show that the relation between intramolecular noncovalent interactions, A–H···B and A–Li···B, and the π-electron delocalization in the sequence of π-conjugated covalent bonds linking A and B can be considered in terms of the Hammett-like substituent effect in which electron-donating and electron-withdrawing properties of substituents are affected by the noncovalent interaction.

- Rotary Molecular Motors: A Large Increase in Speed through a Small Change in Design
  Fernández Landaluce, T.; London, G.; Pollard, M. M.; Rudolf, P.; Feringa, B. L. *J. Org. Chem.* **2010**, *75*, 5323–5325.
  Abstract:



Reducing the steric interaction between the upper-half and the lower-half of a light-driven rotary molecular motor by decreasing the size of the aromatic moiety in the upper-half from a naphthalene to a benzothiophene results in an almost 3500 times faster rotation.

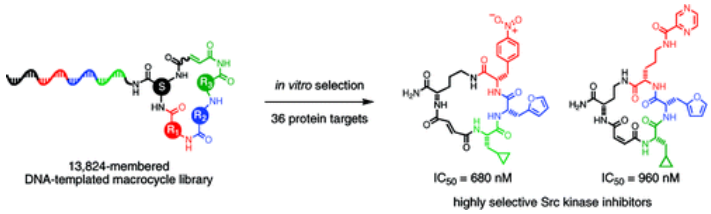
- Orthogonal Covalent and Noncovalent Functionalization of Cyclodextrin-Alkyne Patterned Surfaces
  González-Campo, A.; Hsu, S.-H.; Puig, L.; Huskens, J.; Reinhoudt, D. N.; Velders, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 11434–11436.
  Abstract:



The creation of cyclodextrin patterns on a fluorescent reporter surface by microcontact printing provides a versatile orthogonal surface modification method. The alkyne-β-cyclodextrin surface is prepared through a “click” reaction on alkyne-terminated coumarin monolayers. The resulting

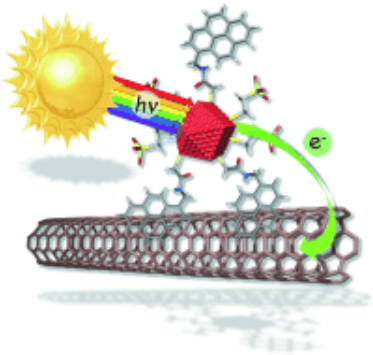
alkyne-β-cyclodextrin surface can be functionalized through supramolecular microcontact printing on cyclodextrin host patterns and by reactive microcontact printing-induced click chemistry on the alkyne-terminated patterns. The orthogonal covalent and supramolecular "host–guest" functionalization of the surface, and its specificity as well as selectivity, is demonstrated by sequential and one-step printing procedures.

- *In Vitro* Selection of a DNA-Templated Small-Molecule Library Reveals a Class of Macrocyclic Kinase Inhibitors
  Kleiner, R. E.; Dumelin, C. E.; Tiu, G. C.; Sakurai, K.; Liu, D. R. *J. Am. Chem. Soc.* **2010**, *132*, 11779–11791.
  Abstract:



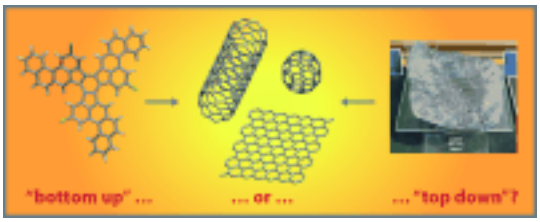
DNA-templated organic synthesis enables the translation of DNA sequences into synthetic small-molecule libraries suitable for *in vitro* selection. Previously, we described the DNA-templated multistep synthesis of a 13 824-membered small-molecule macrocycle library. Here, we report the discovery of small molecules that modulate the activity of kinase enzymes through the *in vitro* selection of this DNA-templated small-molecule macrocycle library against 36 biomedically relevant protein targets. DNA encoding selection survivors was amplified by PCR and identified by ultra-high-throughput DNA sequencing. Macrocycles corresponding to DNA sequences enriched upon selection against several protein kinases were synthesized on a multimilligram scale. *In vitro* assays revealed that these macrocycles inhibit (or activate) the kinases against which they were selected with IC_{50} values as low as 680 nM. We characterized in depth a family of macrocycles enriched upon selection against Src kinase, and showed that inhibition was highly dependent on the identity of macrocycle building blocks as well as on backbone conformation. Two macrocycles in this family exhibited unusually strong Src inhibition selectivity even among kinases closely related to Src. One macrocycle was found to activate, rather than inhibit, its target kinase, VEGFR2. Taken together, these results establish the use of DNA-templated synthesis and *in vitro* selection to discover small molecules that modulate enzyme activities, and also reveal a new scaffold for selective ATP-competitive kinase inhibition.

- Innovative Inorganic–Organic Nanohybrid Materials: Coupling Quantum Dots to Carbon Nanotubes
  Schulz-Drost, C.; Sgobba, V.; Gerhards, C.; Leubner, S.; Krick Calderon, R. M.; Ruland, A.; Guldi, D. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 6425–6429.
  Abstract:



Inorganic meets organic: Covalent bonds (peptide condensation) and noncovalent interactions (π–π stacking) have been employed en route toward versatile donor–acceptor inorganic–organic nanohybrids, QD-pyrene/SWNT. A charge-transfer event within the hybrid transforms the excitonic state of the quantum dot into a charge-transfer state that has a lifetime of several nanoseconds.

- Nanostructured Carbonaceous Materials from Molecular Precursors
  Hoheisel, T. N.; Schrettl, S.; Szilluweit, R.; Frauenrath, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 6496–6515.
  Abstract:



Nanostructured carbonaceous materials, that is, carbon materials with a feature size on the nanometer scale and, in some cases, functionalized surfaces, already play an important role in a wide range of emerging fields, such as the search for novel energy sources, efficient energy storage, sustainable chemical technology, as well as organic electronic materials. Furthermore, such materials might offer solutions to the challenges associated with the on-going depletion of nonrenewable energy resources or climate change, and they may promote further breakthroughs in the field of microelectronics. However, novel methods for their preparation will be required that afford functional carbon materials with controlled surface chemistry, mesoscopic morphology, and microstructure. A highly promising approach for the synthesis of such materials is based on the use of well-defined molecular precursors.