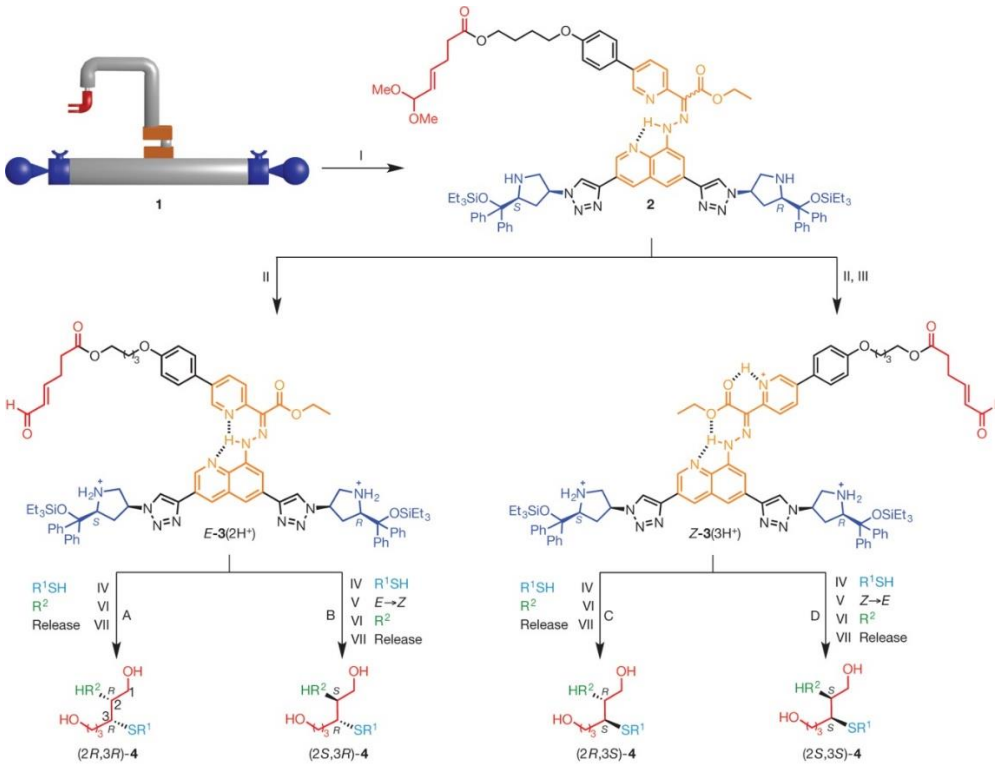
Fabiana Ciocchetti, 04/10/2021

Stereodivergent synthesis with a programmable molecular machine

Kassem, S. et al. *Nature* 549, 374–378 (2017)



Who are the corresponding authors and what are their research areas?

David Leigh (University of Manchester, GB). Leigh's group is interested in molecular machinery, molecular ratchet mechanisms, molecular knots, molecular assemblers, and molecular robotics.

What is the main claim of the article?

Leigh's group has developed a molecular robot that moves a substrate between different activating sites to achieve different product outcomes from chemical synthesis.

The molecular robot comprises a central skeleton responsible for movement (pH responsive), of a base with two identical sites at the ends but having the opposite chiral configuration, and of an arm to which the substrate is bound. The substrate (α,β-unsaturated aldehyde) reacts with one of the two chiral centers and gives rise to a diastereoisomer. All four diastereoisomers can be obtained through four different programs. What differentiates one program from another is the presence or absence of all operations and the order in which they are carried out.

Reaction sequences are carried out in one pot, and the robot can be programmed to produce selectively each isomer of the product, including compounds that cannot be made through conventional organocatalysis.

I think the beauty of this article is in two different aspects.

The first is to obtain all four possible isomers without recourse to a stereoselective synthesis or chiral resolution.

The second is the idea and its potential. Now it is used to synthesize a molecule, but it could for example be exploited to facilitate the proximity between two molecules or to move or remove molecules from the reaction environment. Future generations of programmable molecular machines may play significant roles in chemical synthesis and molecular manufacturing.

How is it demonstrated?

For each program (A-D), the conversions and diastereomeric and enantiomeric ratios of the product mixture were determined by ^{1}H NMR spectroscopy and chiral high-performance liquid chromatography (HPLC) and compared to authentic standards of each of the four possible stereoisomers. Each of the four stereoisomers is the major product of a different program of the molecular machine.

What are the typical experimental conditions?

The programs were performed at relatively dilute (mM) concentrations of the machine in order to favor intra-machine over intermolecular reactions. Representative example: stereoselective synthesis of *(2R,3R)*-4 through program A of molecular machine. Stages reagents and conditions: II. CF_3COOH (2.2 equiv.), r.t., 10 min, >99% conversion; IV. $HS(CH_2)_2(CF_2)_7CF_3$ (R^1 SH, 100 equiv.), 0 °C, 30 h, >99% conversion; VI. $H_2CC(SO_2Ph)_2$ (R^2, 200 equiv.), 0 °C, 24 h; VII. $NaBH_4$, MeOH, 0 °C, 2 h, CD_2Cl_2 (1 mM), then $LiAlH_4$, THF, −78 °C to r.t., 1 h.

Which are the key related papers?

- Pick-up, transport and release of a molecular cargo using a small-molecule robotic arm
  Kassem, S., Lee, A. T. L., Leigh, D. A., Markevicius, A. & Solà, J. *Nat. Chem.* 8, 138–143 (2016).
- Dynamic Control of Chiral Space in a Catalytic Asymmetric ReactionUsing a Molecular Motor
  Wang, J. & Feringa, B. L. *Science* 331, 1429–1423 (2011)
- "There's plenty of room at the bottom". The transcript of the classic talk that Richard Feynman gave on December 29th 1959 at the annual meeting of the American Physical Society at the California Institute of Technology (Caltech) was first published in the February 1960 issue of Caltech's Engineering and Science, which owns the copyright. It has been made available on the web at
  http://www.zyvex.com/nanotech/feynman.html

Additional comments, including additional elements of interest

What I liked most is that once the robot molecular skeleton is engineered, the whole process is performed simply by varying the pH and the protonation state of the hydrazone. The greatest difficulty is in the step of imagining the structure of the robot and its realization. Each component must be selected carefully for the overall operation of the machinery. Once the robot is made, however, you can free your imagination and synthesize various molecules with the same device.