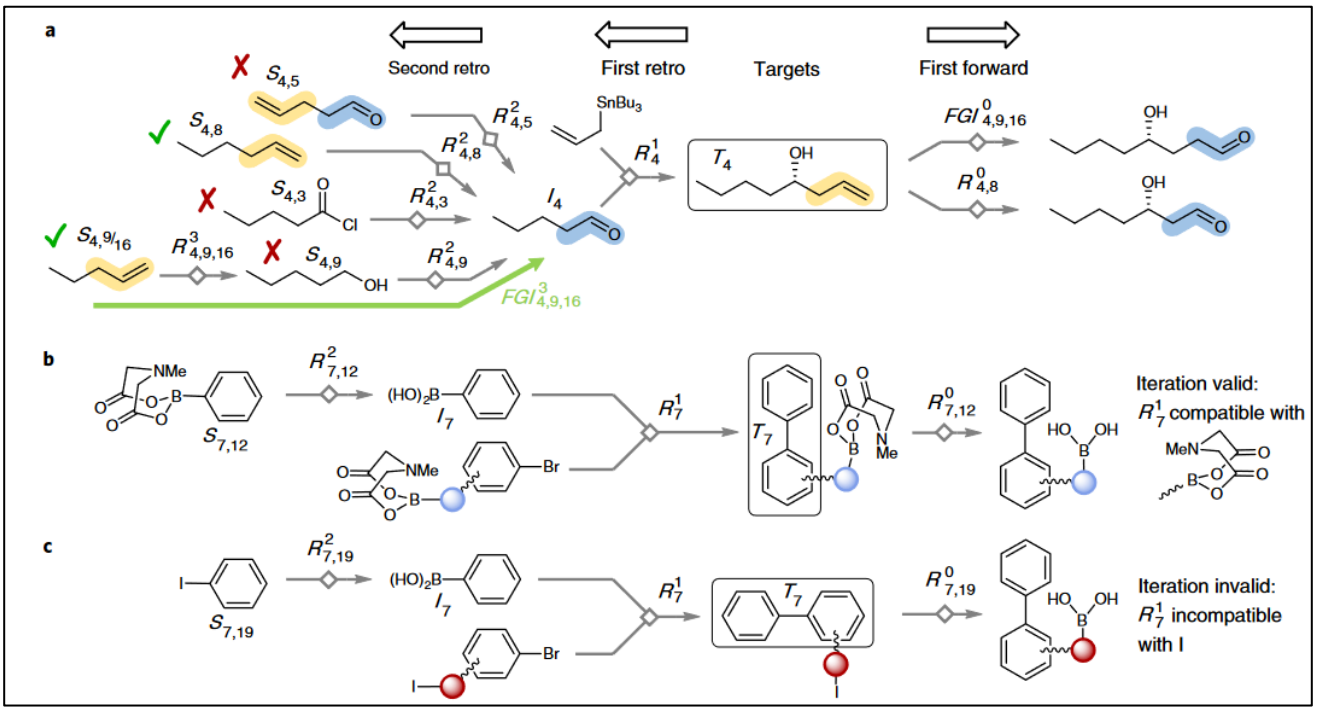
Víctor Sabanza Gil, April 2022

A computer algorithm to discover iterative sequences of organic reactions

Nat. Synth. **1**, 49-58 (2022)



Algorithm design principle and explanation of iterative sequences

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

The corresponding authors are Prof. Bartosz Grzybowksi and prof. Jacek Młynarski. The first is a world leading researcher in the field of artificial intelligence and network theory applied to synthetic chemistry, whereas the second is interested in asymmetric catalysis and the application of AI to this field.

What is the main claim of the article?

They show that it is possible to discover iterative sequences of organic reactions without serendipity using an algorithm that only uses information about individual reactions.

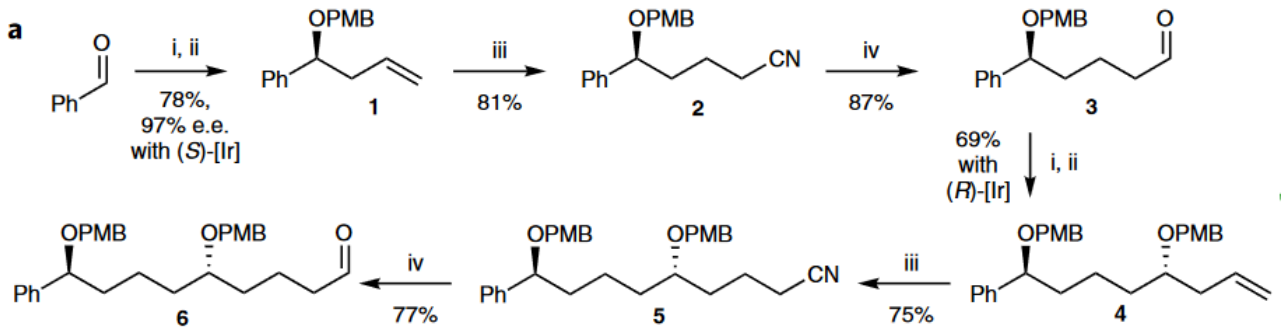
Nature Synthesis is a new journal (established in 2022) that is focused on chemical and material synthesis as well as enabling technological innovations. This article was published in its first issue.

How is it demonstrated?

First, high-quality reaction rules are defined (they include typical reaction conditions and incompatible functional groups). Then, the algorithm is defined. In a nutshell, it applies retrosynthetic transformations to a starting material and checks if certain requirements are fulfilled. Finally, the algorithm is applied to different substrates generating around half-million sequences, clustering them according to the type of transformation (thousands of transformations are obtained).

What are the typical experimental conditions?

Concerning the algorithm, its working principles have been already described. Some of the discovered sequences are experimentally validated, but the experimental conditions depend on the specific type of sequence. An example of one of the discovered sequences is shown below, which generates a 1,5-dihydroxy motif via asymmetric allylation, hydrocyanation and nitrile reduction.



i) allyl acetate, Krische's iridium catalyst ((S)- or (R)SEGPHOS, 4-cyano-3-nitrobenzoate ligated), Cs2CO3, iPrOH, THF, 100 °C, 16–18 h; ii) PMBCl, NaH, TBAI, DMF, 0 °C to r.t., 17–20 h; iii) Zn(CN)2, NiCl2·6H2O, dppp, Zn, DMAP, H2O, MeCN, 80 °C, 22–24 h; iv) DIBAL-H, DCM, −78 °C to r.t., 1.5–2 h;

Which are the key related papers?

Angew. Chem. Int. Ed. **51**, 1 – 6 (2012): algorithmic discovery of one-pot reactions

Science **369**, eaaw1955 (2020): application of network theory and algorithms to the discovery of prebiotic chemical reaction sequences

Additional comments, including additional elements of interest

The algorithm not only discovers new sequences of iterative reactions but also previously known sequences where some of the reagents have been changed for others with the same role. Therefore, it is coherent with the previous chemical knowledge and it allows to expand this knowledge by discovering previously unknown transformations.