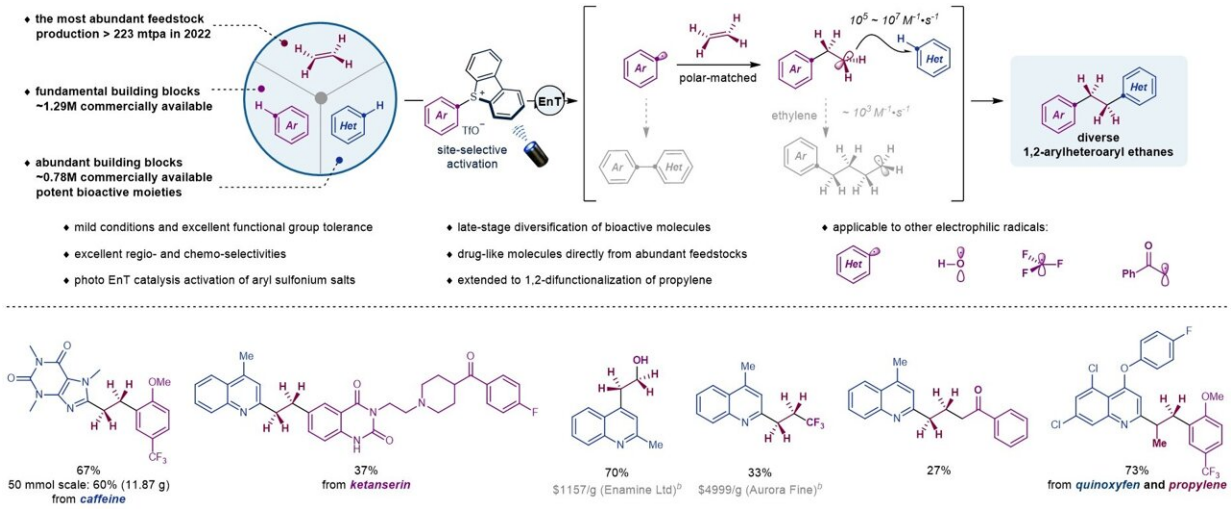
Chemists develop modular approach for creating important class of pharmaceutical compounds

July 17 2024



Overview of the modular approach using fundamental feedstock chemicals, ethylene, arenes, and heteroarenes for assembling potential drug-like molecules. The lower section of the visual showcase examples of 1,2-arylheteroaryl ethanes produced using this method, highlighting quick access of pharmaceutical derivatives. Credit: *Nature Chemistry* / National University of Singapore

Chemists at the National University of Singapore (NUS) have developed a modular approach to create 1,2-arylheteroaryl ethanes, a class of compounds important for drug discovery and pharmaceutical development, using fundamental feedstock chemicals such as ethylene,

arenes and heteroarenes.

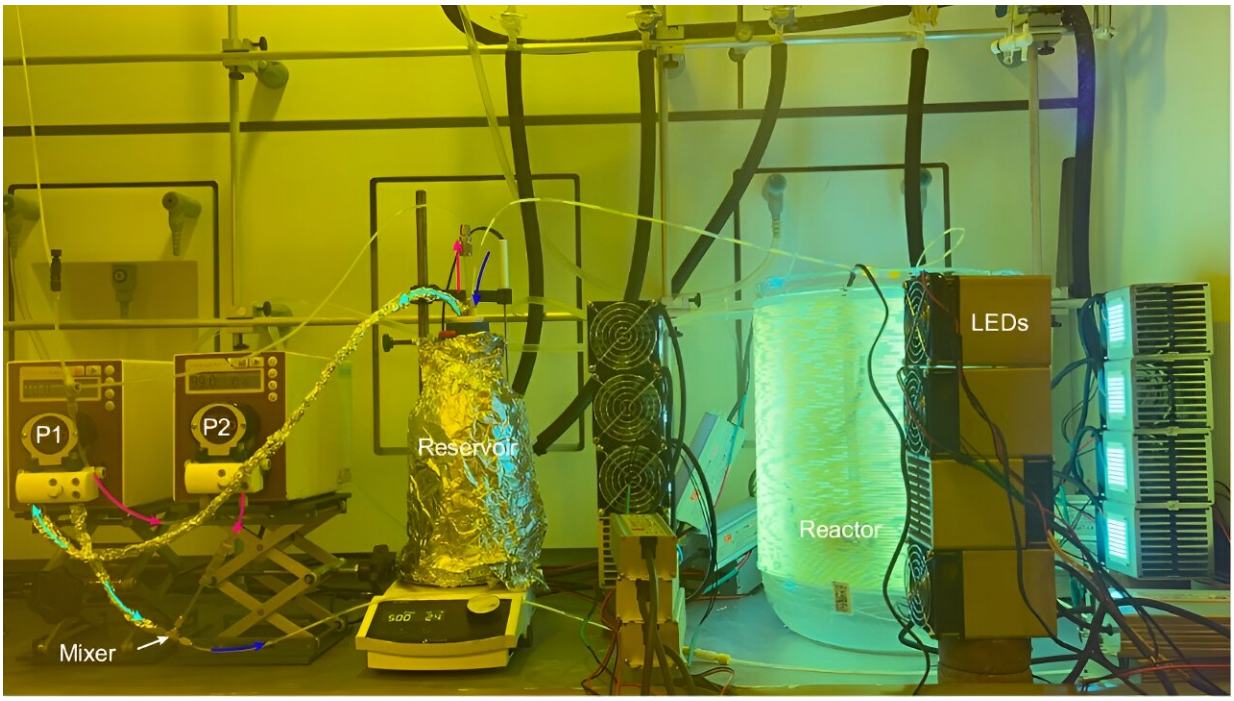
The findings have been published in the journal *Nature Chemistry*.

Advancing organic synthesis, particularly in pharmaceuticals, relies on achieving molecular diversity through the strategic assembly of basic feedstocks. By harnessing these feedstock chemicals, researchers can explore new synthetic pathways, improve chemical reactions, and tailor molecular structures specifically for drug development.

The 1,2-arylheteroaryl ethane structures are particularly promising for pharmaceutical applications, as evidenced by an extensive catalog of over 49,000 documented compounds, with approximately 31% showing utility in various bioactivity studies.

Despite their potential, traditional synthesis methods face challenges such as reliance on pre-functionalized synthons, lengthy synthetic routes, limited substrate compatibility and demanding reaction conditions, especially when synthesizing complex structures.

On the other hand, ethylene, a cornerstone of the global chemical industry, had a production volume of over 223 million tons in 2022, underscoring its key role as a primary feedstock. Additionally, arenes and heteroarenes molecules serve as fundamental and widely available sources of aryl and heteroaryl chemical groups.



In-house circulation-flow reactor (picture taken with a yellow filter for clarity). Credit: *Nature Chemistry* (2024). DOI: 10.1038/s41557-024-01560-7

This raises the question of whether these valuable chemicals can be modularly assembled from abundant and basic feedstock chemicals which are readily available.

Associate Professor Wu Jie and his research team from the Department of Chemistry at NUS have addressed this challenge with a new approach. Their success is based on an application that uses light to initiate the generation of aryl radicals from aryl sulfonium salts.

Aryl radicals are reactive intermediates and involved in many organic reactions. These radicals then react with ethylene and heteroarenes molecules to form the required chemical compound.

This method not only facilitates the synthesis of 1,2-arylheteroaryl ethanes but also allows for the production of other valuable fine chemicals by using different radical precursors, gaseous alkenes (ethylene and propylene), and heteroarenes molecules.

This significant advancement in using gaseous alkenes and coupling multiple fundamental components could greatly impact the drug discovery and petrochemical industries by enabling the modular and sustainable production of diverse molecular scaffolds. A simple in-house built circulation flow system has been employed to add practicality to this synthetic protocol.

Prof Wu said, "Our long-standing interest in synthesizing valuable fine chemicals from fundamental feedstock chemicals, particularly natural gases, has led us to develop innovative, on-demand assembly strategies. These methods have the potential to substantially impact both the pharmaceutical and petrochemical industries."

More information: Tao Liu et al, Modular assembly of arenes, ethylene and heteroarenes for the synthesis of 1,2-arylheteroaryl ethanes, *Nature Chemistry* (2024). DOI: 10.1038/s41557-024-01560-7

Provided by National University of Singapore