ICIQ

Institute of Chemical Research of Catalonia

HTE

High Throughput Experimentation

ACCELERATING YOUR RESEARCH IN CHEMISTRY

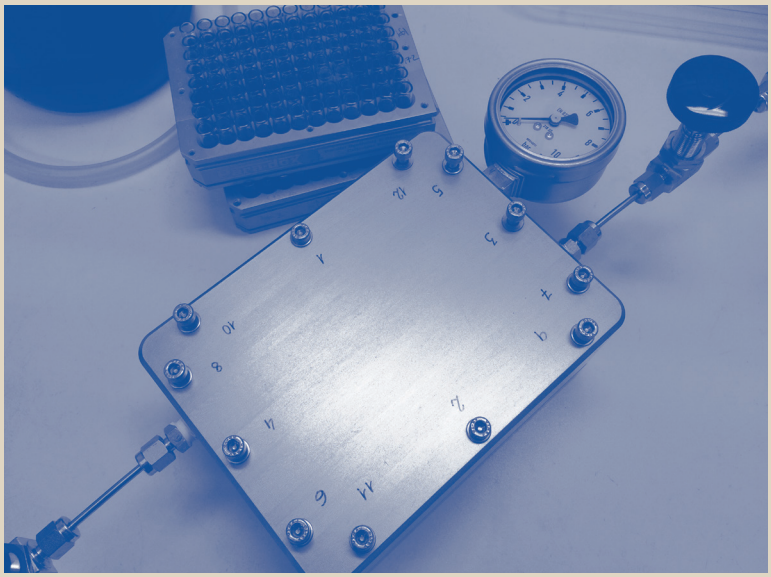
WHY HIGH THROUGHPUT EXPERIMENTATION (HTE) AT ICIQ?

High Throughput Experimentation (HTE) is a powerful tool to **accelerate the discovery and implementation of new and efficient methodologies**. It allows to rapidly develop the best conditions for a specific reaction.

KNOWLEDGE-BASED EXPERIMENTAL DESIGN + **FORCED SERENDIPITY** + **PARALLELIZATION**

KEY FEATURES

- 100% HTE focused synthesis and analytical facilities
- Small-scale, yet good reproducibility (100 µL reaction volume)
- Save costs on expensive starting materials
- Statistical support for an optimized and cost-effective design of experiments (DoE)
- In-house reactor design and fabrication (pressure reactor technology, photochemical reactors)
- Extensive library of catalysts (over 400 ligands)
- Broad range of reaction types, including:
  - Air sensitive reactions (equipment to work under strict inert conditions: <0.1 ppm O_2 and H_2O),
  - Reactions with reactive gases
  - Photochemical reactions
  - Reactions under high pressure conditions



In-house developed photoreactor which allows to work under a pressure up to 10 bar and different wavelengths

COMPLEMENTARY R&D SERVICES AT ICIQ?

ICIQ offers a wide range of R&D services to the fine chemicals and pharmaceutical industry which can be used in combination with the HTE platform to further develop the results:

- Process optimization to multi-gram scale, both in **batch** or **flow** system
- **Crystallization** screenings and crystallization process optimization
- Design of experiments **(DoE)** and **industrial expertise**

BENEFIT FROM THE SCIENTIFIC EXCELLENCE OF A LEADING RESEARCH INSTITUTE

Depending on a project's focus, one or more of ICIQ's leading scientists can act as scientific advisors.

The Institute of Chemical Research of Catalonia (ICIQ) is an international leading institution in the field of **catalysis**. ICIQ holds over 200 researchers in 19 research groups. We publish on average 170 papers per year, 86% of the them in journals within the top 25% of journals with highest impact factor. ICIQ has obtained 16 ERC (European Research Council) grants.

ICIQ's industrial partners include companies such as Syngenta, Covestro (former Bayer MaterialScience), Henkel or Esteve Pharmaceuticals.

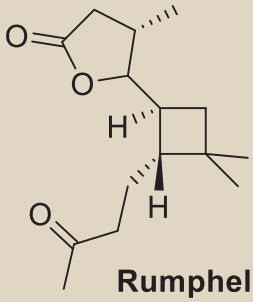
WHO CAN BENEFIT FROM HTE?

FINE CHEMICAL INDUSTRY

When employed in chemical research, HTE is frequently used to examine arrays of reaction conditions to quickly determine the preferred catalyst, reagents, and solvents to use for a given transformation. In this context, these tools are equally powerful **for optimizing individual steps in a total synthesis** or as **a driver for discovery of novel methodology**.

APPLICATION EXAMPLES

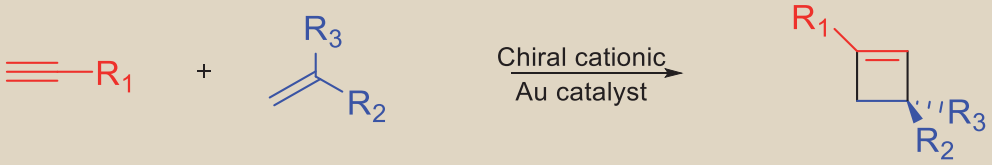
APPLICATION EXAMPLE: ENANTIOSELECTIVE TOTAL SYNTHESIS OF RUMPHELLAONE A



Rumphellaone A

Rumphellaone A has been isolated from the gorgonian coral *Rumphella antipathies* and shows cytoxicity against certain leukemia tumors

HTE METHODS WERE USED TO IDENTIFY THE OPTIMAL CATALYTIC SYSTEM FOR THE [2+2] CYCLOADDITION STEP



The enantioselective gold(I)-catalyzed reaction of terminal alkynes with alkenes leads to cyclobutenes by a [2+2] cycloaddition, which are valuable synthons for the preparation of functionalized cyclobutanes present in a variety of natural products and pharmaceuticals.

J. Am. Chem. Soc. **2017**, 13628-13631. **A. M. Echavarren Research Group (ICIQ)**

HTE SET-UP

- Reactions were set-up in a **glovebox** (O_2 and H_2O < 5 ppm)
- **Micromole scale** allows for minimal material requirement: 100 µL reaction volume
- A **library of pre-dosed chiral ligands** in reaction vials allows for a rapid screening : 180 chiral ligands available in the HTE lab

FAST WORK-UP AND ANALYSIS

- **UHPLC analysis** to determine conversion and yield **(3 min per sample)**
- **Chiral SFC** analysis to determine enantiomeric excess **(4 min per sample)**

DATA MANAGEMENT

- **Analytical Studio Software** from Virscidian allows **for fast data processing**

WHO CAN BENEFIT FROM HTE?

PHARMACEUTICAL AND LIFE-SCIENCE INDUSTRY – DISCOVERY PHASE

A powerful application of HTE combines arrays of reactants under a small set of conditions to make large **collections of compounds**, with applications in medicinal chemistry or materials science. These tools have also been used to **demonstrate generality and functional group tolerance of new reactions**, elucidate reaction mechanisms, evaluate process absorbents, among others.

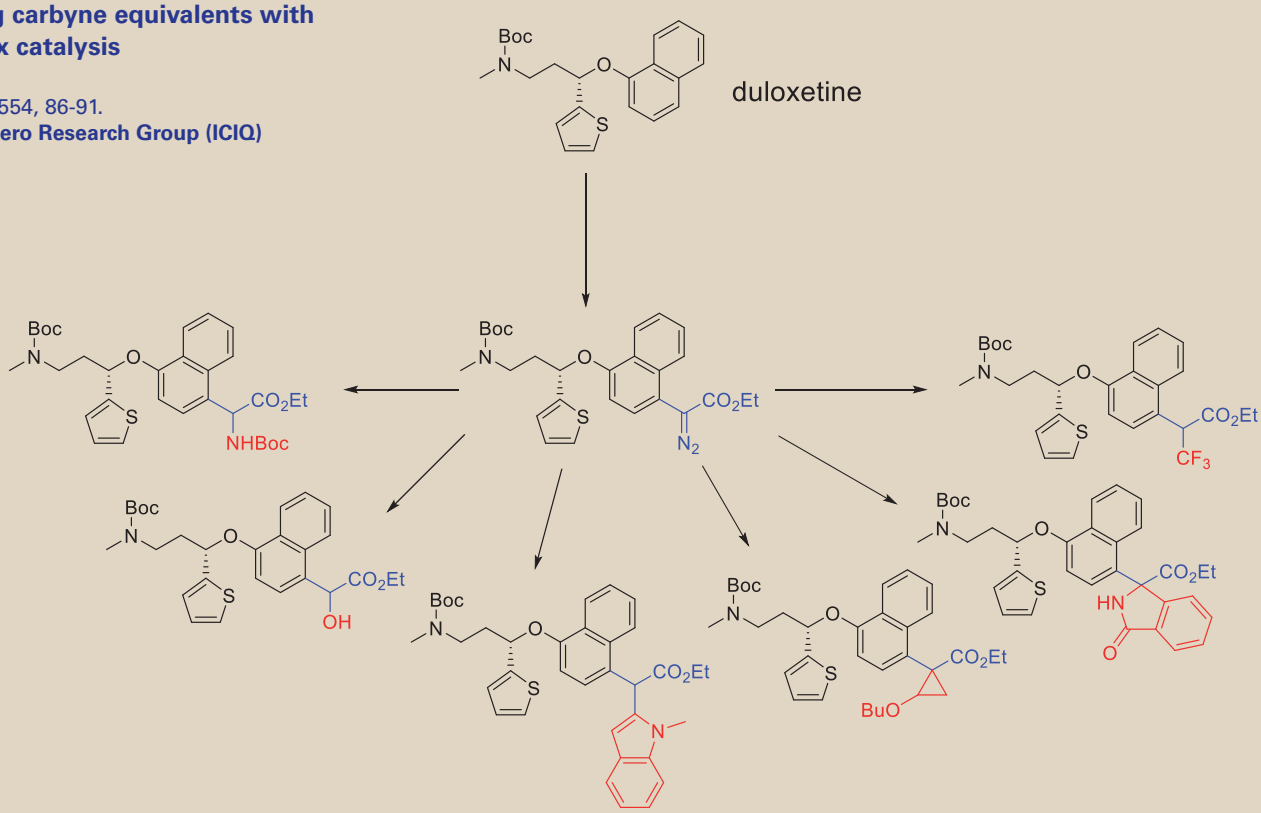
The late-stage functionalization (LSF) of advanced synthetic intermediates and drug candidates has emerged as an important strategy for contemporary drug discovery. Introducing small, inert functionality to a pharmacophore of interest relatively late in the discovery process may address problems associated with on- and off-target activity, metabolism, and pharmacokinetic profile.

APPLICATION EXAMPLES

LATE-STAGE FUNCTIONALIZATION OF AN ACTIVE INGREDIENT

Generating carbyne equivalents with photoredox catalysis

Nature **2018**, 554, 86-91.
M. Garcia Suero Research Group (ICIQ)



HIGH THROUGHPUT METHODS CAN BE USED TO GENERATE MOLECULAR DIVERSITY AND LIBRARIES OF STRUCTURALLY DIVERSE ANALOGUES OF ACTIVE INGREDIENTS IN A REDUCED TIME

- **Photocatalytic insertion of a carbene functional group into an aromatic ring** provides a key intermediate for further derivatization
- Standard diazo chemistry allows for further derivatization and creation of molecular diversity
- Other photocatalytic processes for C-H activation of active ingredients have been developed in-house

WHO CAN BENEFIT FROM HTE?

PHARMACEUTICAL AND LIFE-SCIENCE INDUSTRY – DEVELOPMENT & COMMERCIAL PHASE

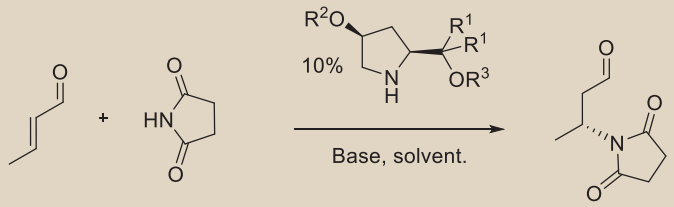
After the identification of a clinical candidate the medicinal chemistry route has to be substituted by a **scalable reaction** sequence to allow the manufacturing of clinical material and later to ensure the commercial supply. There is a tremendous need for identification of a chemical process to produce a high-quality API (impurity profile) in development and commercial scale under consideration of cost-of-goods, and environmental impact (green chemistry)

We can combine the HTE platform with DoE, expertise in process development in the pharmaceutical industry and complementary technologies such as **flow chemistry** and **crystallization**, to offer robust processes with industry acceptable conditions, ready for pilot plant.

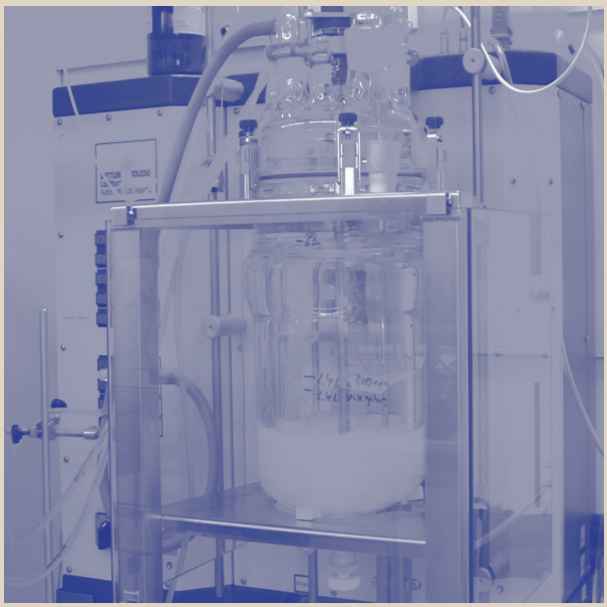
APPLICATION EXAMPLES

HTE-DOE COMBINED APPROACH

The combined use of high throughput experimentation **(HTE)** techniques with **DoE** has led to the identification of a very efficient organocatalytic system for the enantioselective addition of cyclic imides to α, ß-unsaturated aldehydes



Adv.Synth. Catal. **2017**, 359,2414–2424.
M. A. Pericàs Research Group (ICIQ)



VARIABLES OPTIMIZED BY MICROSCALE HTE

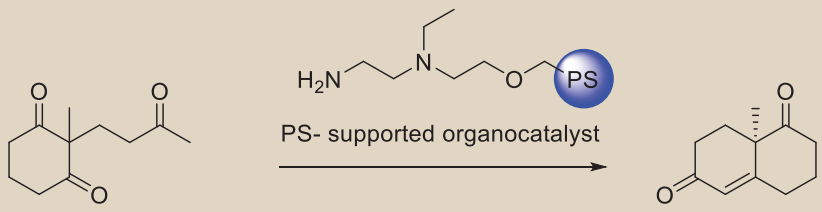
- Non-continuous variables: Organocatalysts, solvents, bases, presence of H_2O

FACTORS STUDIED IN THE DOE

- Continuous variables: Temperature, reaction time, catalyst loading, equiv. of reagents, and reaction concentration.

HTE – DOE OPTIMIZATION FOR A FLOW CHEMISTRY APPLICATION

High Throughput methods were used to identify optimal reaction conditions for Asymmetric Robinson Annulations catalyzed by a Polymer-Supported Catalyst.



The preparation through Robinson annulation of enantiopure building blocks has suffered from important drawbacks, such as the need for high catalyst loading or extremely long reaction times.

ACS Catal. **2017**, *7*, 1383–1391.
M. A. Pericàs Research Group (ICIQ)

- **Microscale HTE** in the optimization stage allows for **minimal consumption of the PS-Catalyst**. Variables optimized: solvents, acids and additives.
- Optimal conditions are **suitable for the continuous production** of a wide range of chiral bicyclic enones under mild conditions, with residence times as short of 10 min (**flow**).
- Factors studied in the **DoE**: Temperature, reaction time, catalyst loading, equiv. of succinimide, equiv. of base , and reaction concentration.

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