

The Novel Innovation towards the *Stereospecific* *Drugs*

Presented by

Applied Chemical and Instrument Co., Ltd.

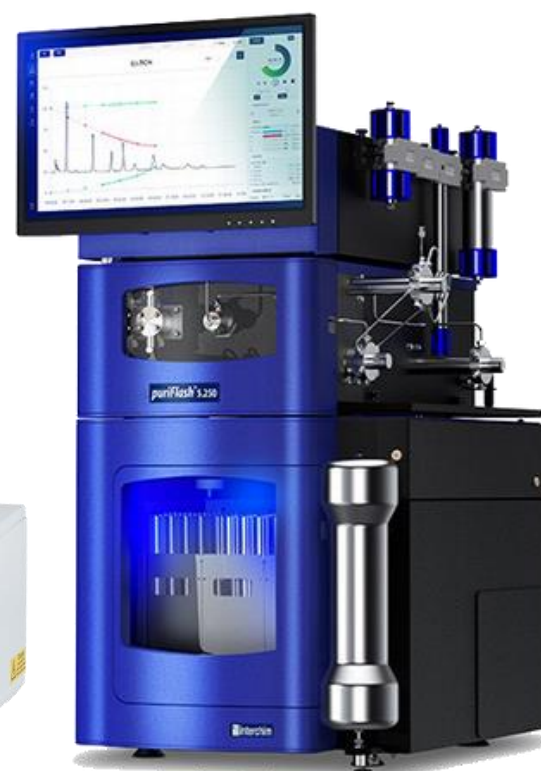
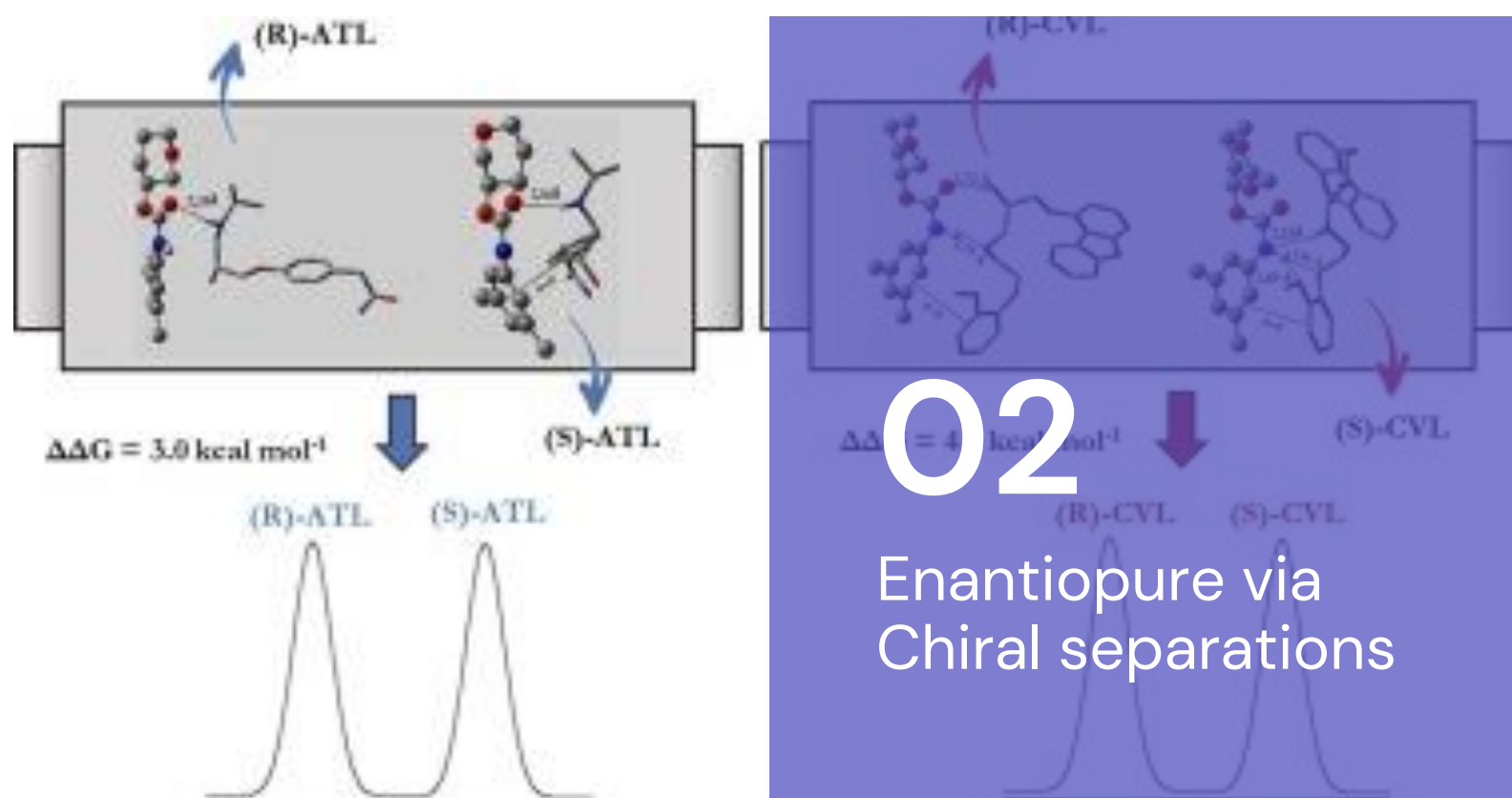
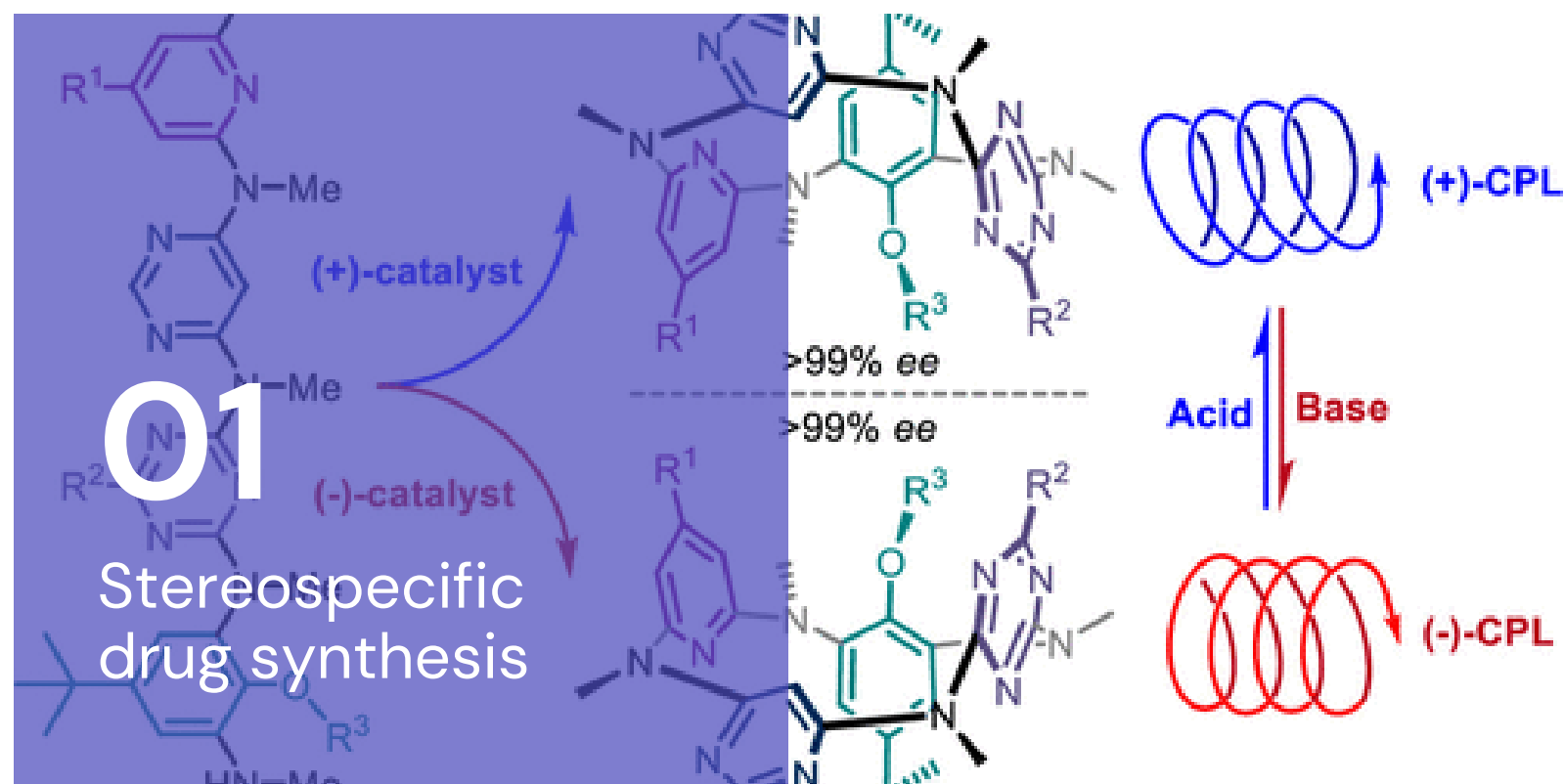


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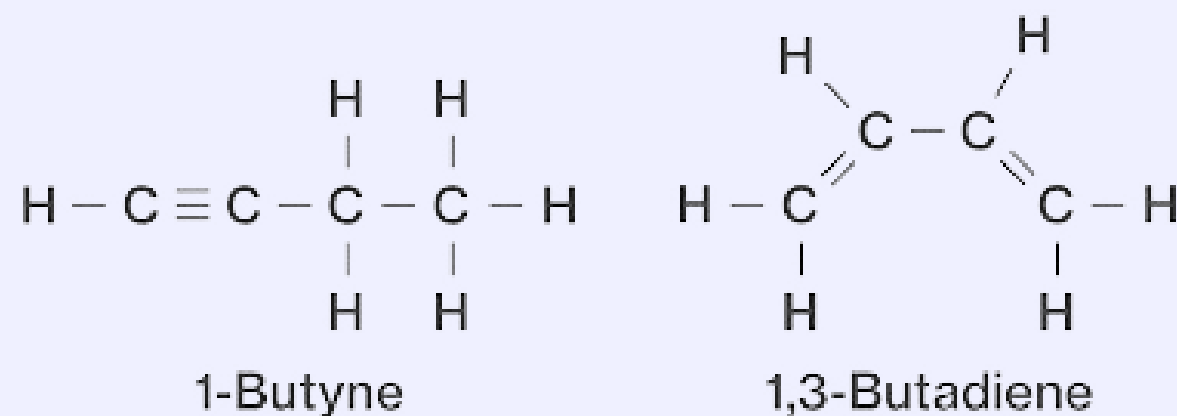
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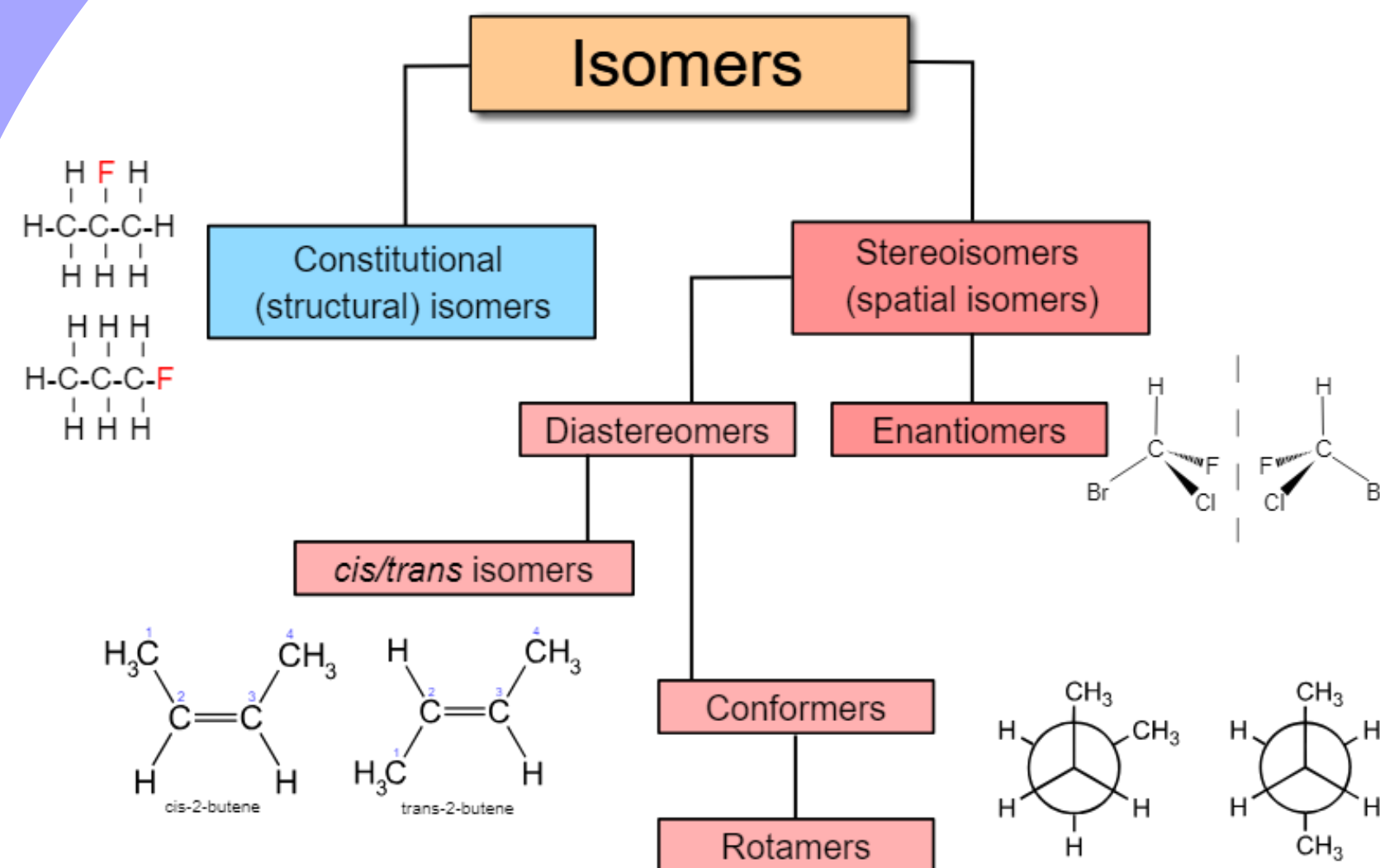
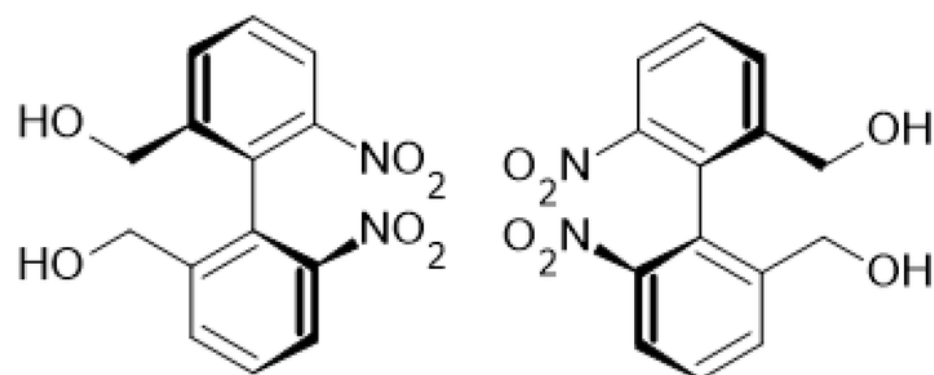
What is "Isomer"?

"Same Chemical formular" but
"have different chemical structure"

Structural Isomer

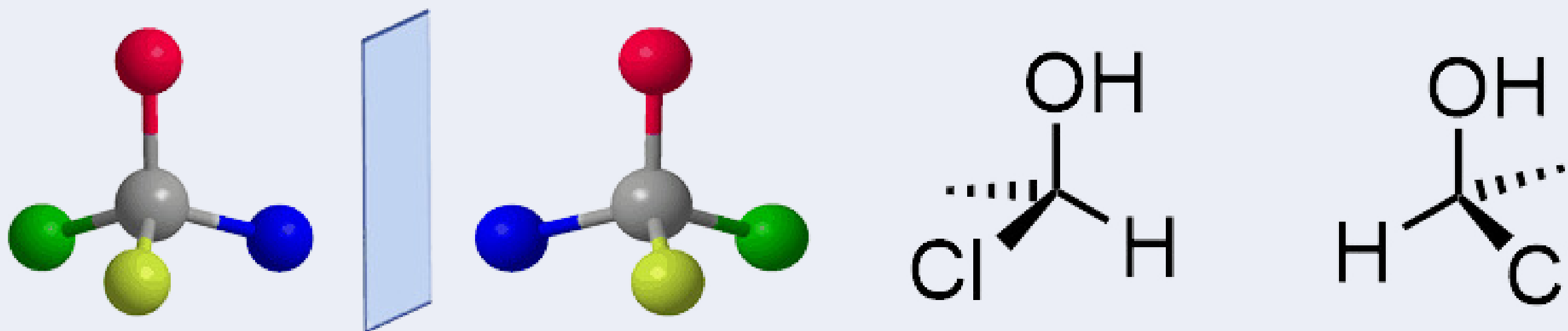


Stereo Isomer

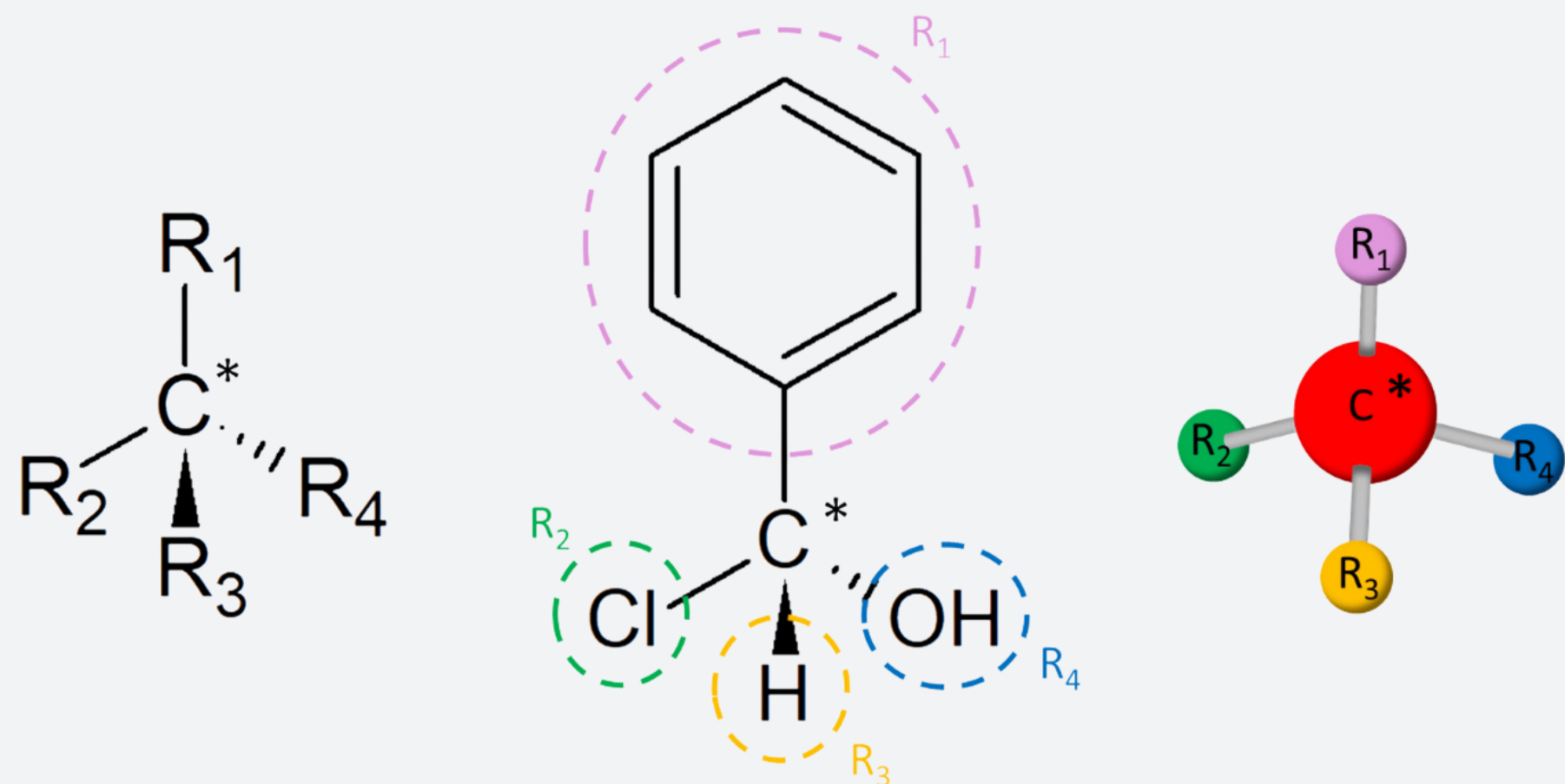


Pairs of Enantiomeric compounds

- Chiral Center
- Mirror image
- No plane of symmetry***



Enantiomers - mirror images

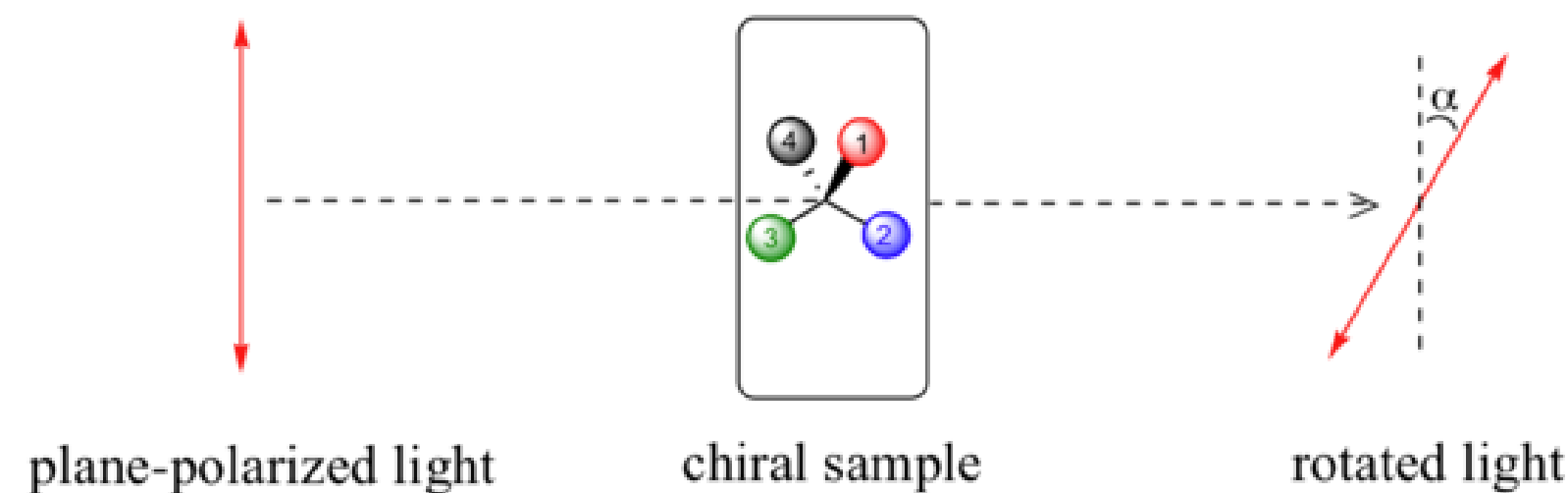
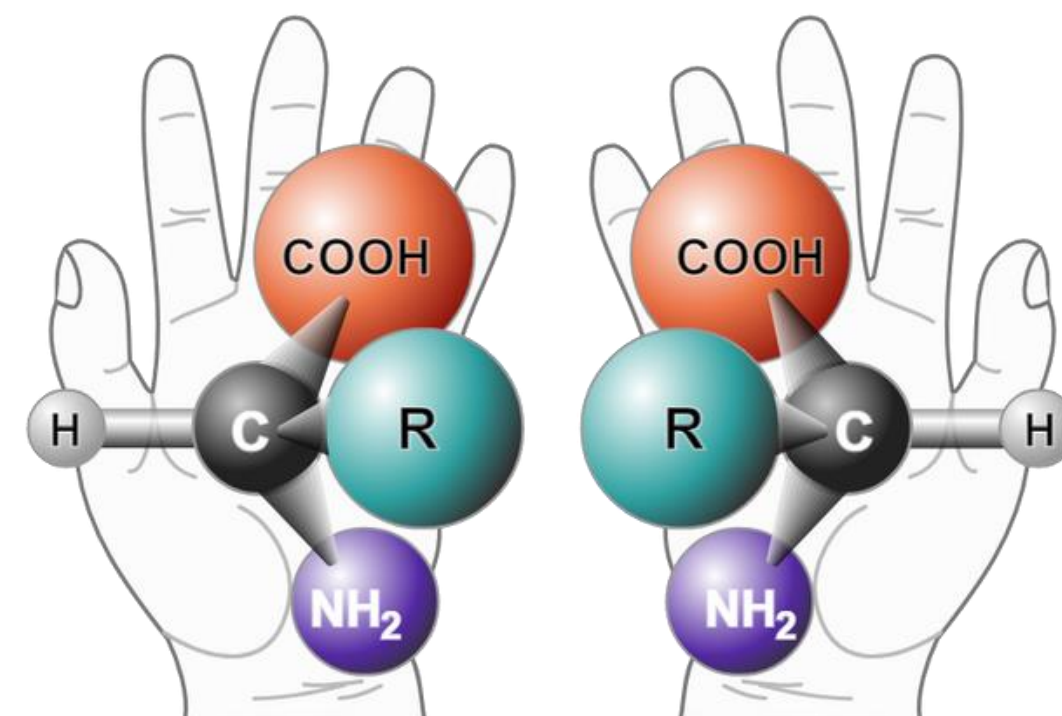


Chiral Molecule

- At least one **tetrahedral atom** bound to four different groups
- Express *optical rotation activity*

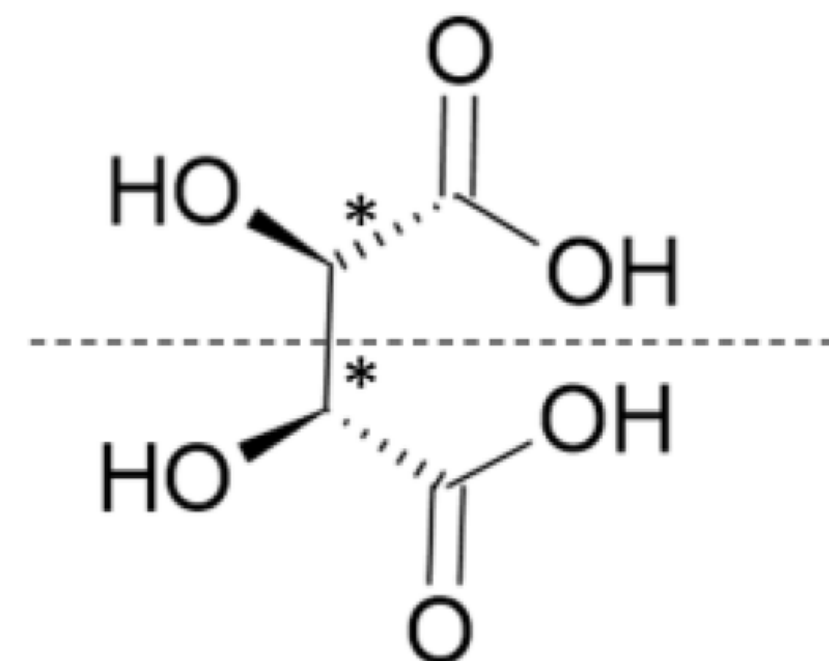
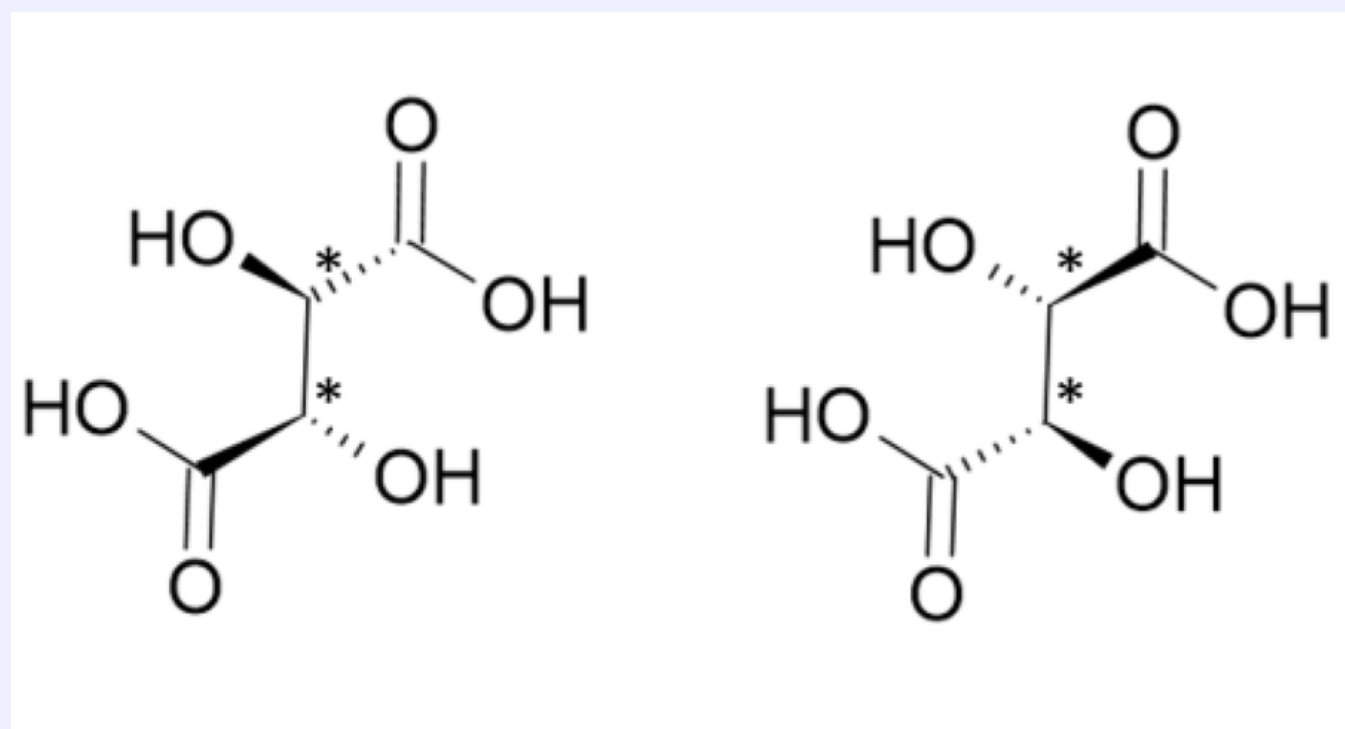
"Chirality"

A non overlapping of molecules



Enantiomer VS Meso isomer

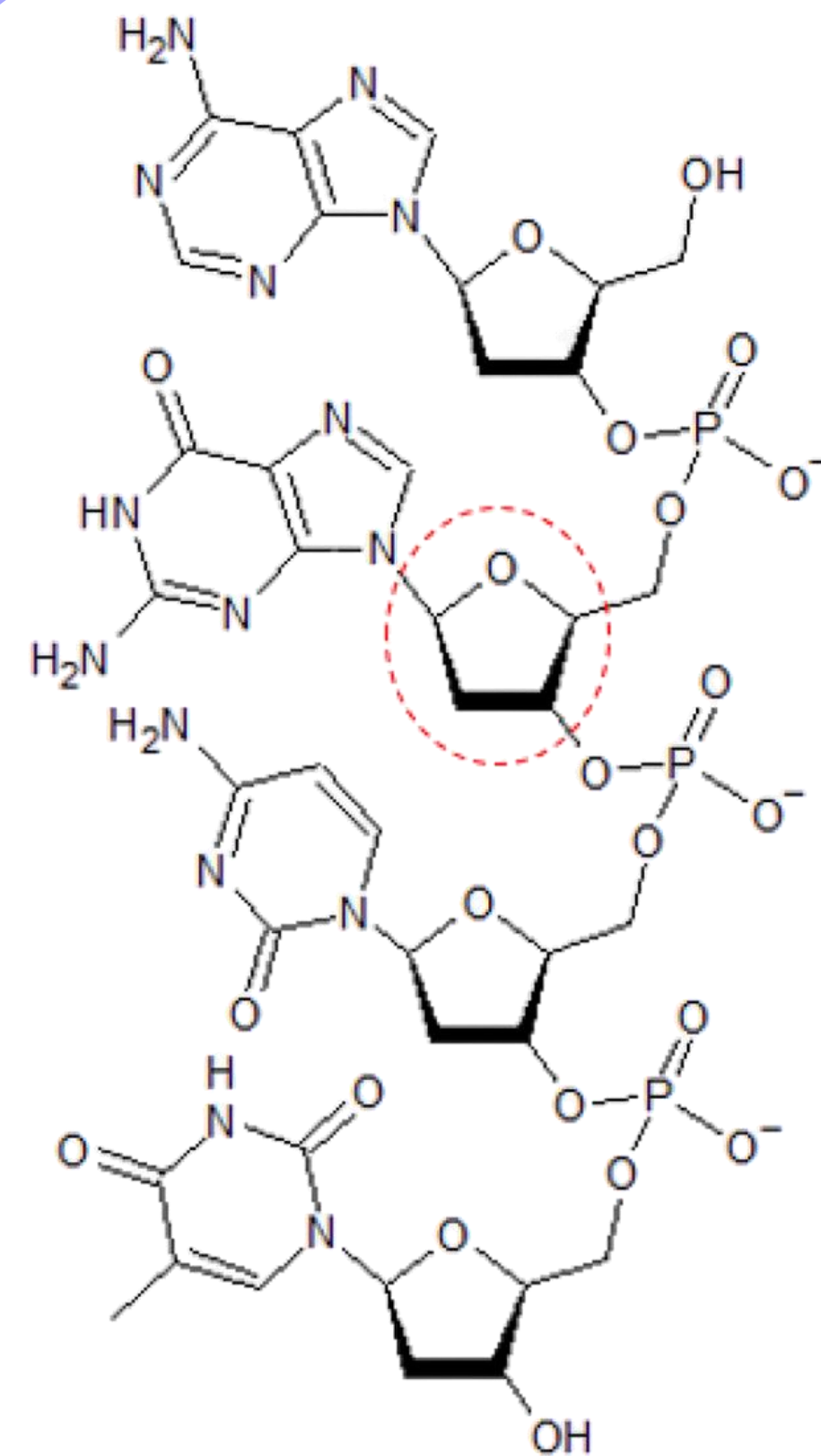
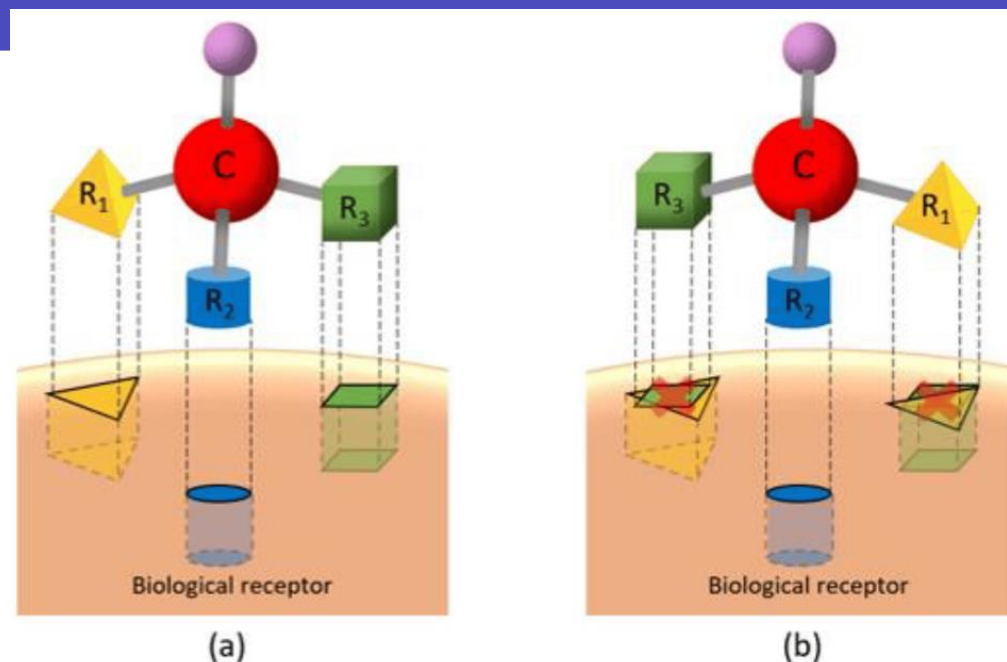
“Molecules with at least two chiral carbons that *present a plane of symmetry are not chiral molecules*”



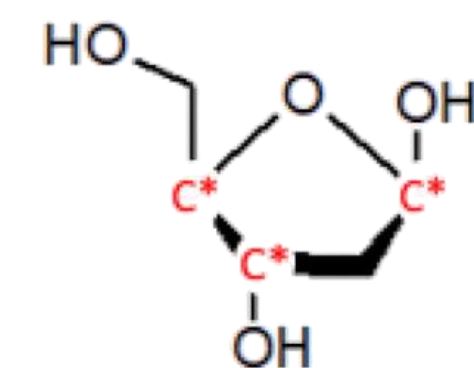
Non optically active stereoisomer !

Enantiomer and Human Body

Chirality represents an intrinsic property of so-called 'Structural blocks of life' such as amino acids, monosaccharides, peptides, proteins and polysaccharides.



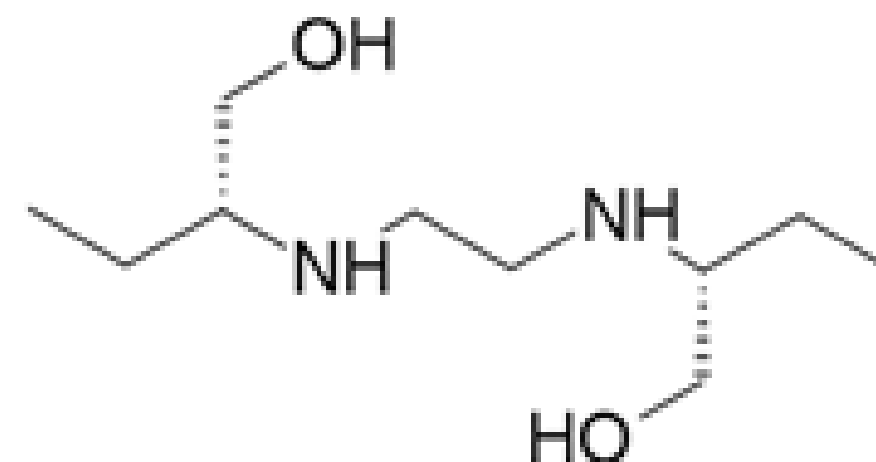
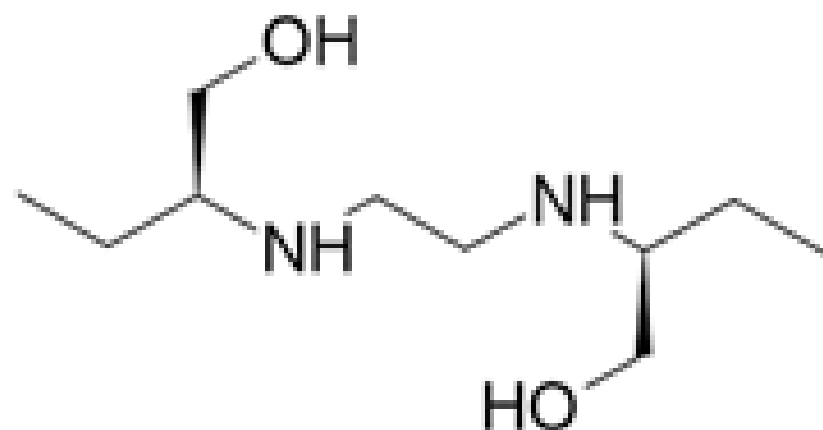
DNA structure



Monosaccharides
deoxyribose

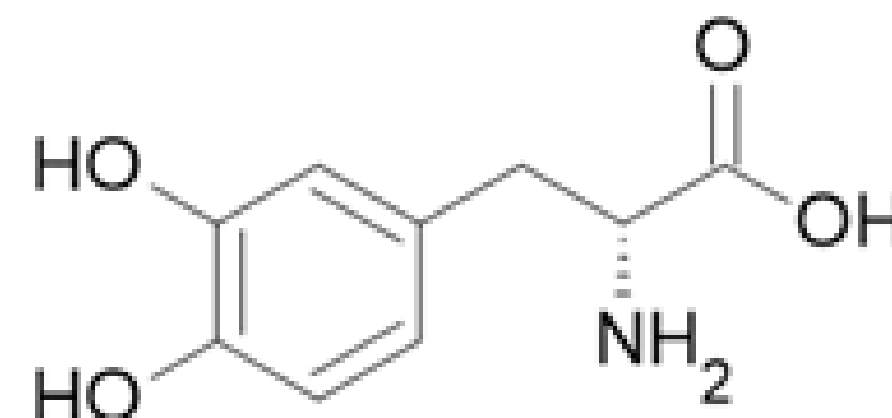
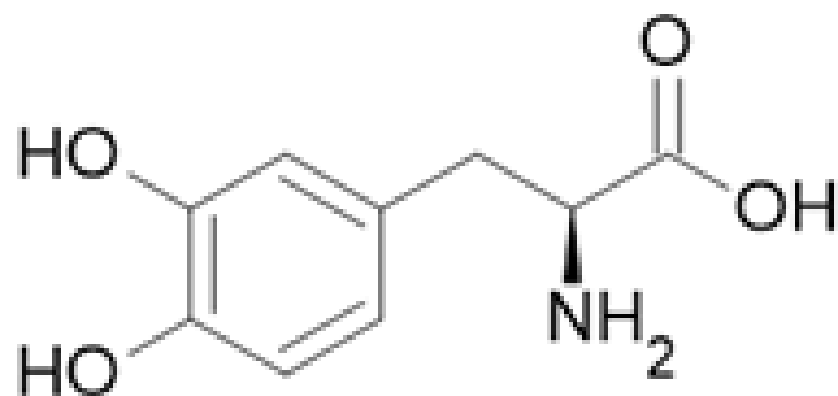
Difference in biological activities between enantiomers

Tuberculostatic



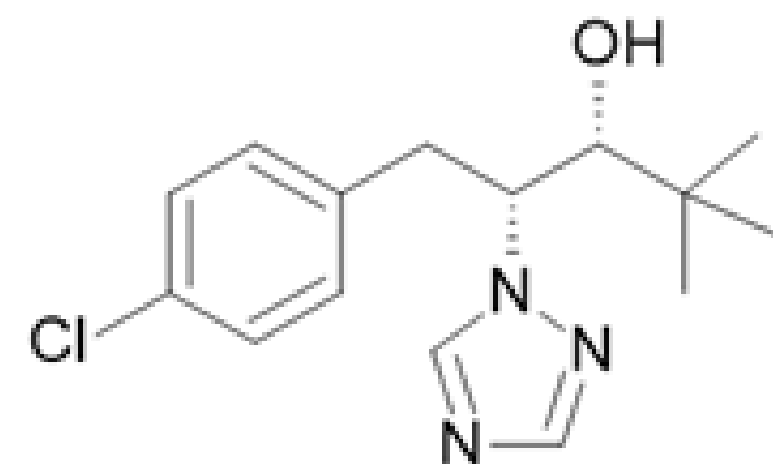
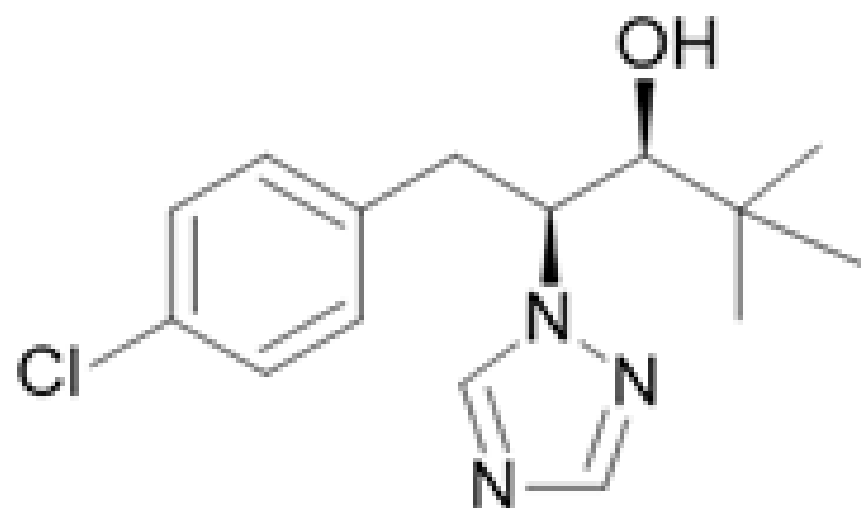
Causes blindness

Anti-Parkinson



Serious side effects

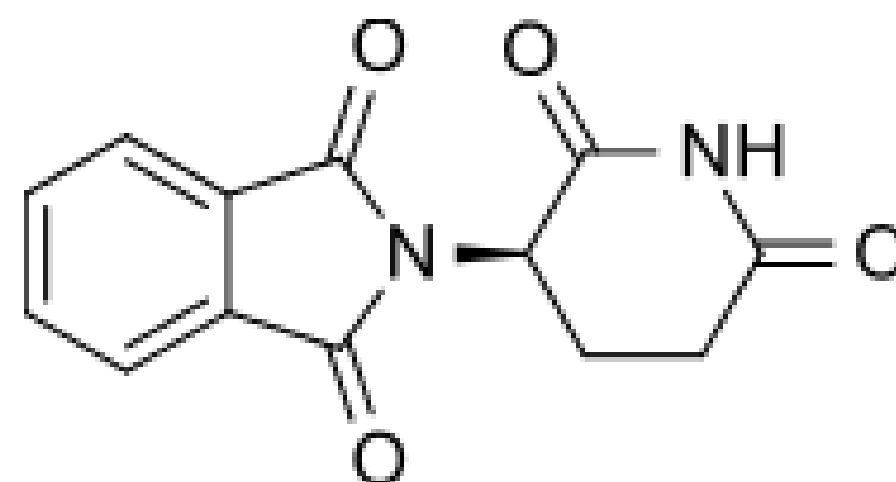
Plant growth regulator



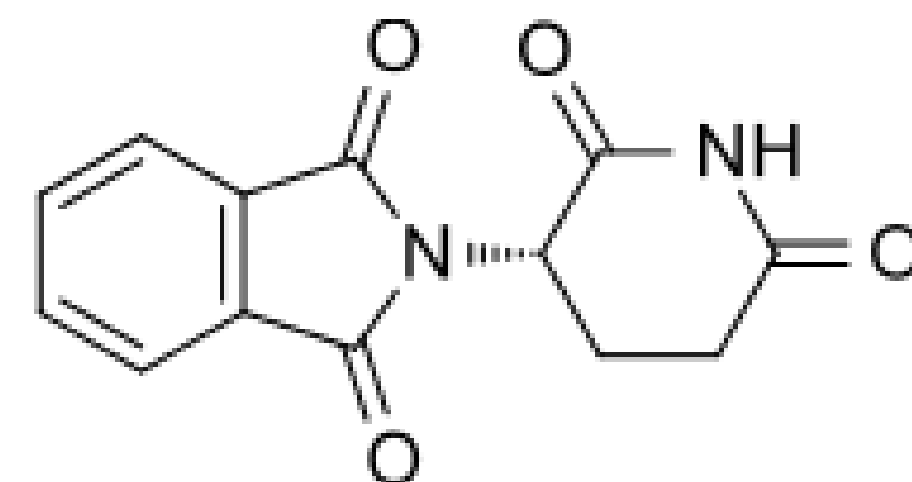
Fungicide

Enantiomeric Drug Market

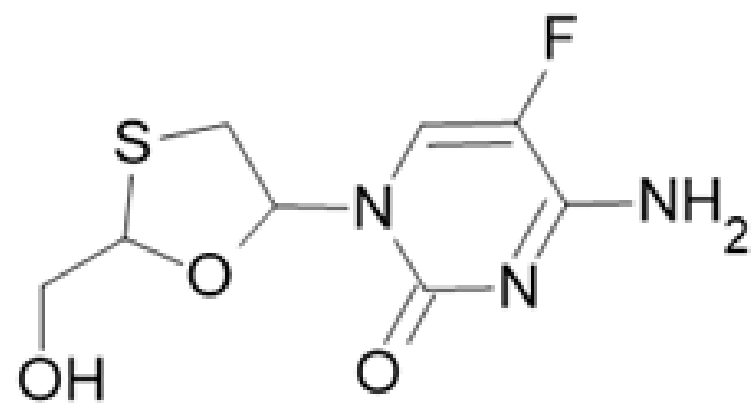
Due to the difference in the performance of different enantiomers, the complexity of some compounds, and the economic-market importance, it is crucial to efficiently and economically obtain each compound separately, either by synthesis or separation.



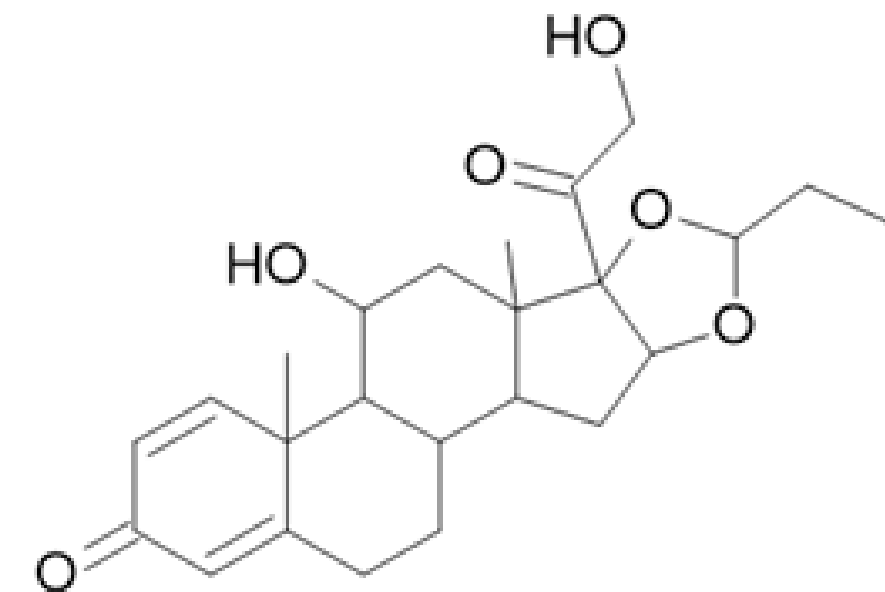
(R)-thalidomide



(S)-thalidomide

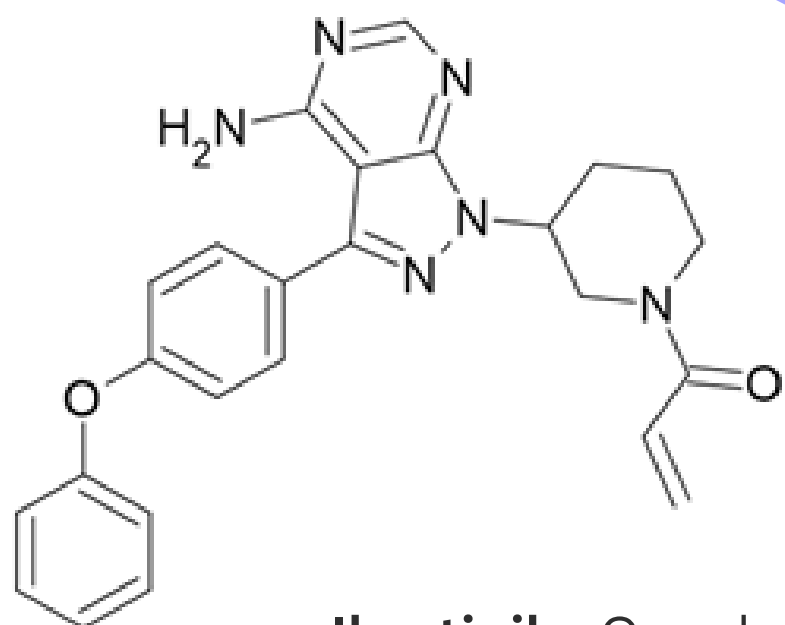


Emtricitabine : Infectious

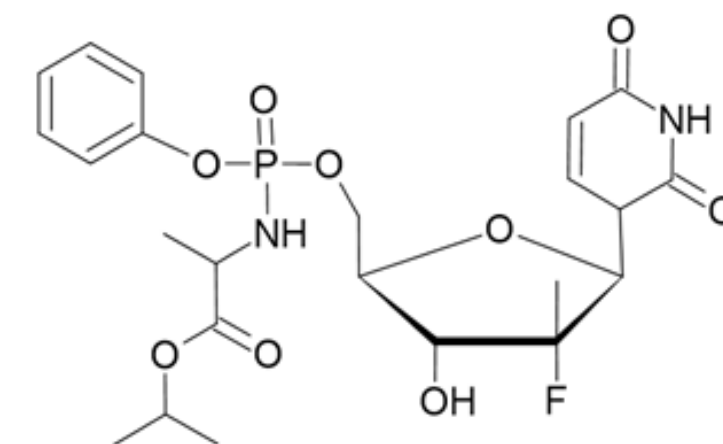


Formoterol : Respiratory Disorders

Top seller chiral drugs worldwide in 2017



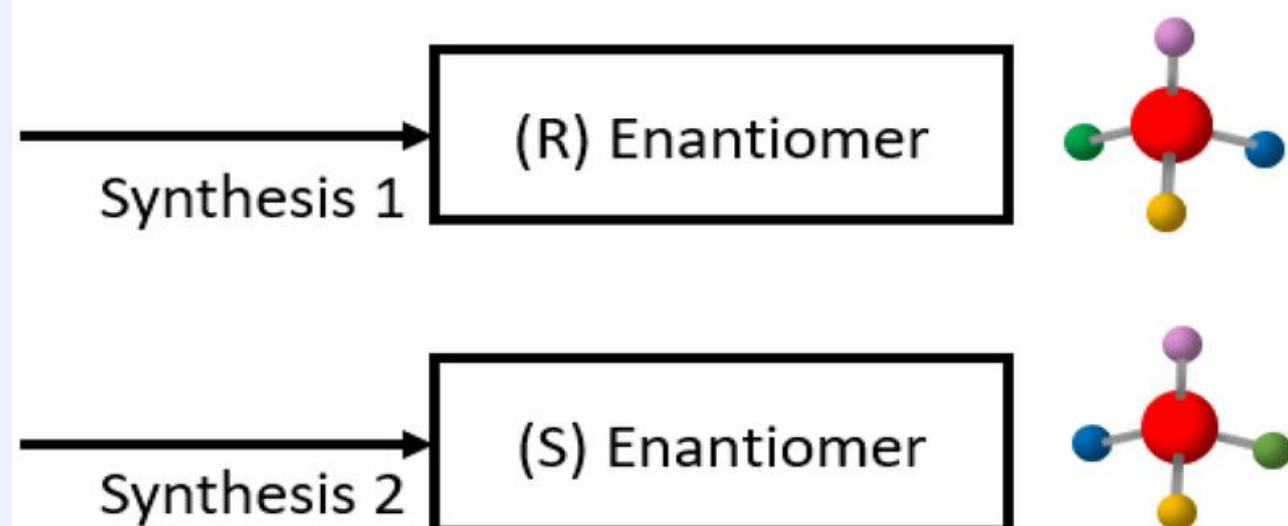
Ibrutinib : Oncology



Sofosbuvir : Infectious Diseases

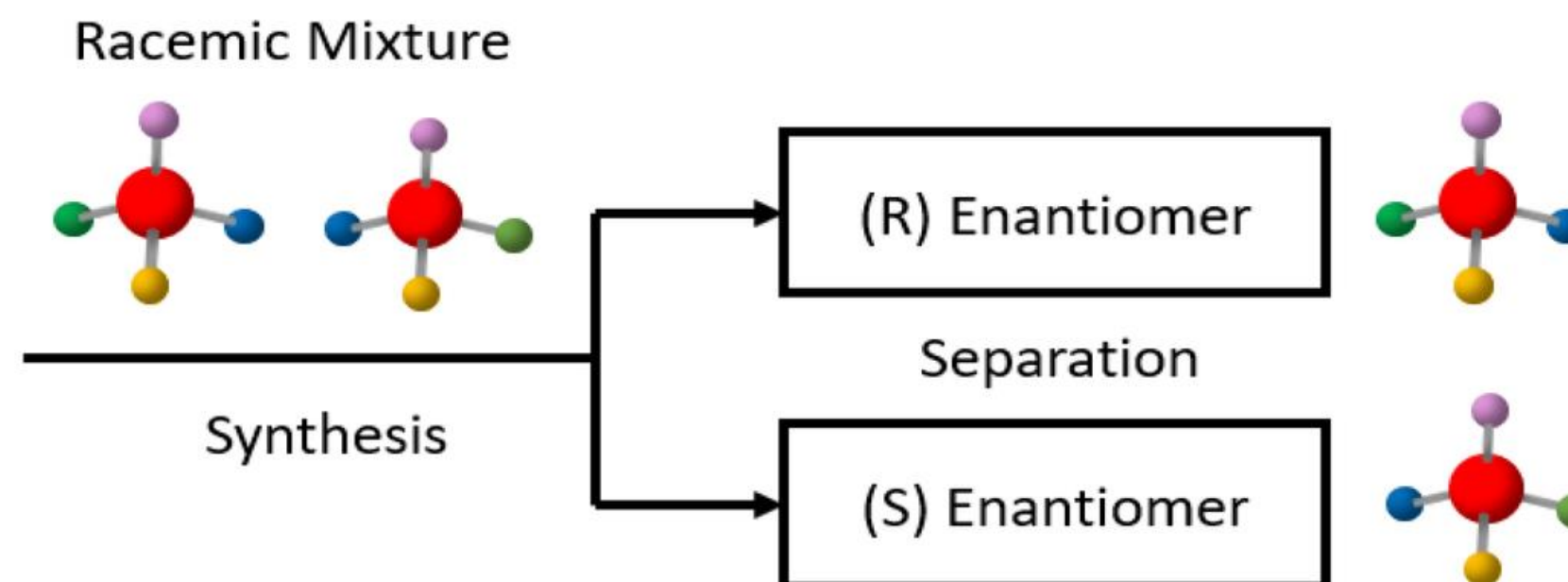
To obtain the pure form of chiral compounds...

Chiral Route Stereoselectivity



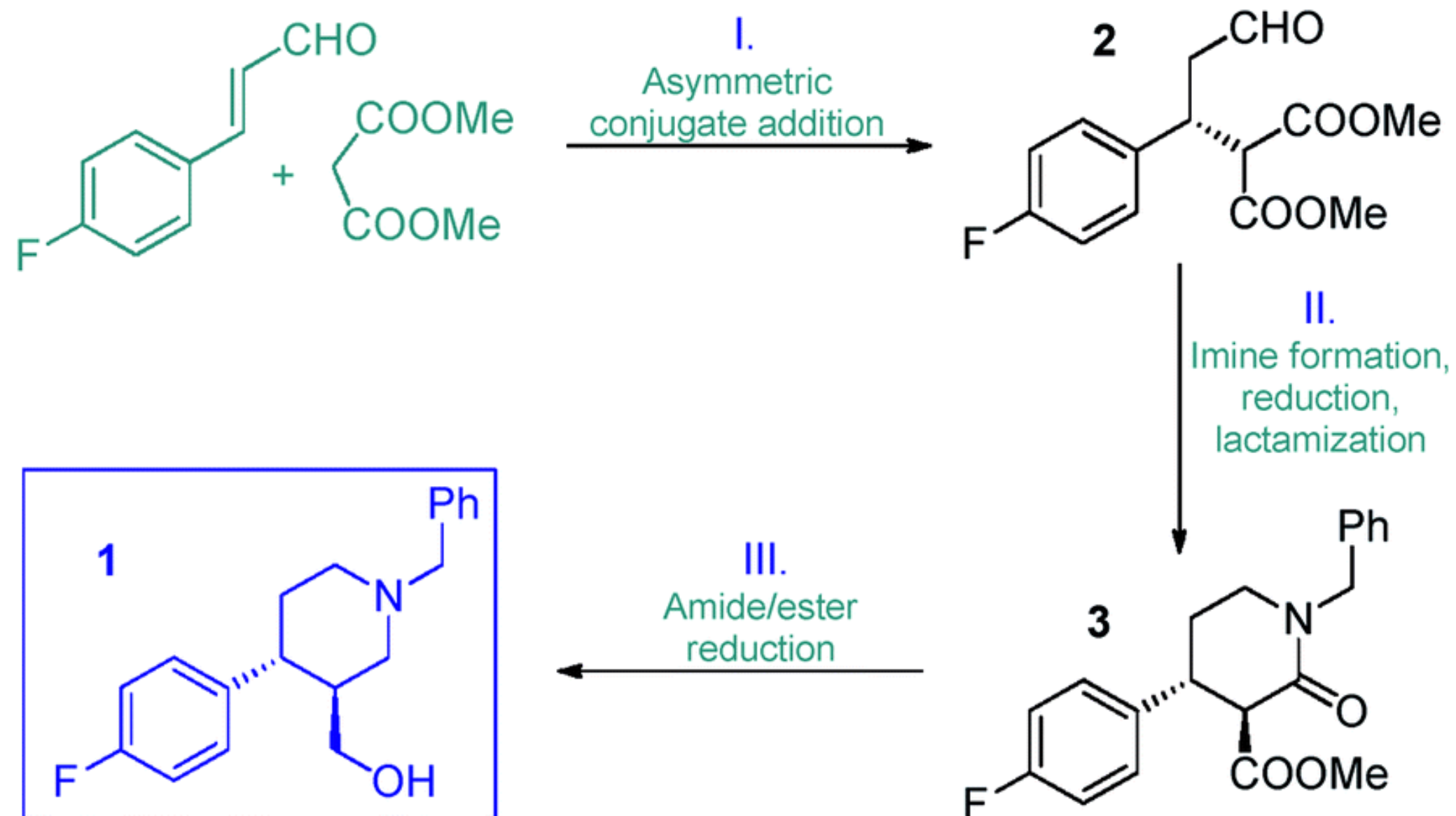
(a)

Racemic Route Racemic Synthesis



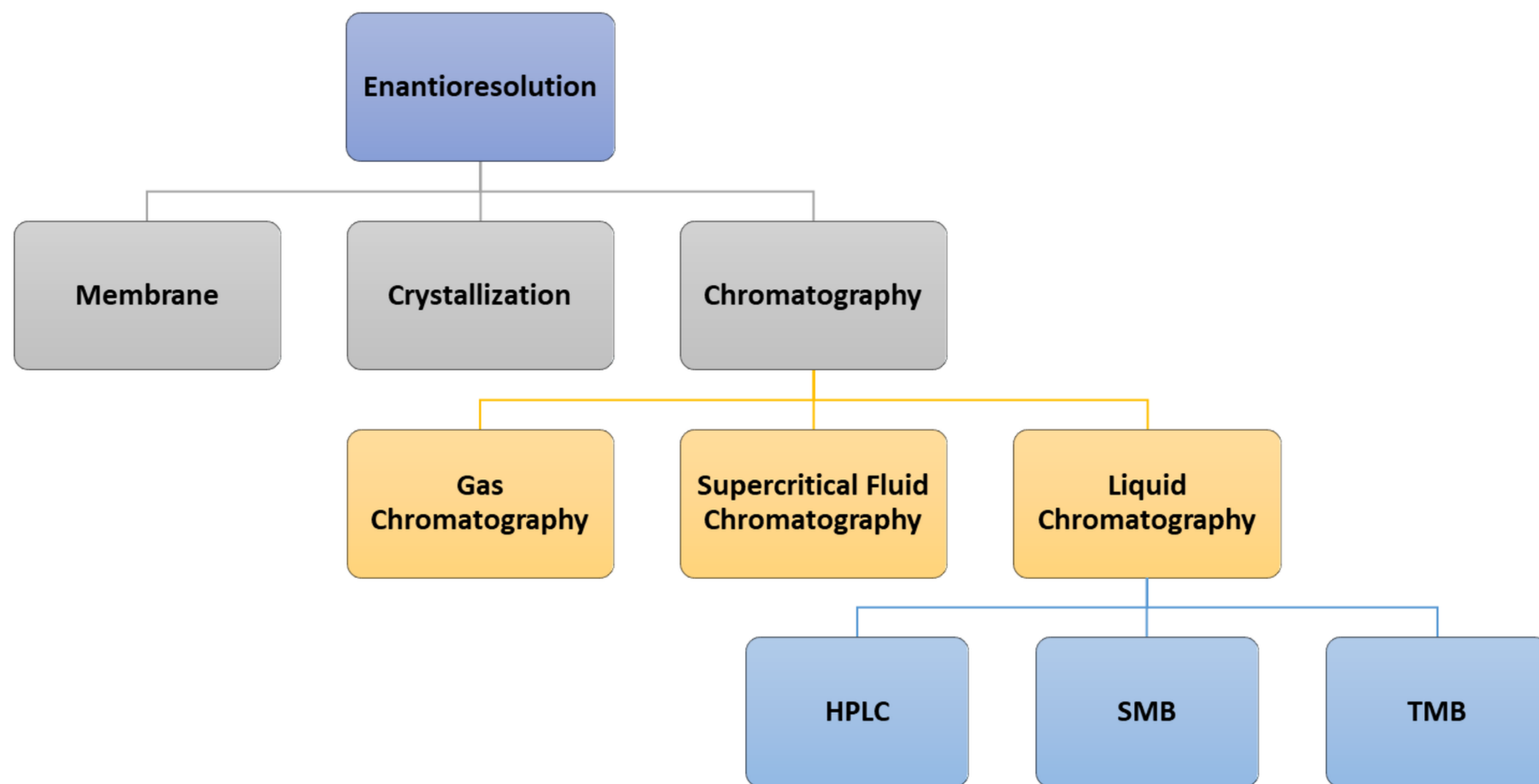
(b)

Chiral drug synthesis

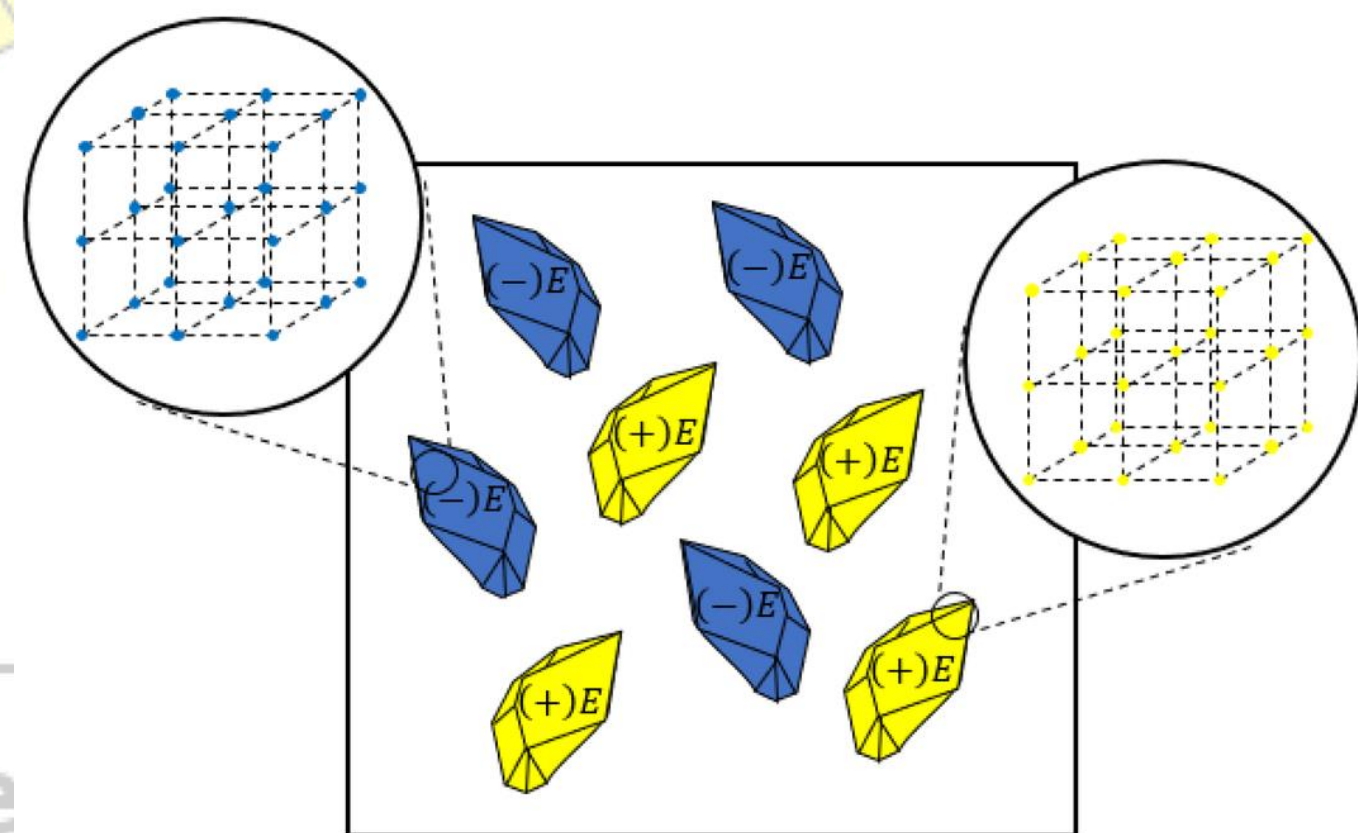




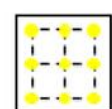
Racemic separation



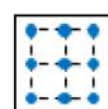
Enantio Resolution : Crystallization



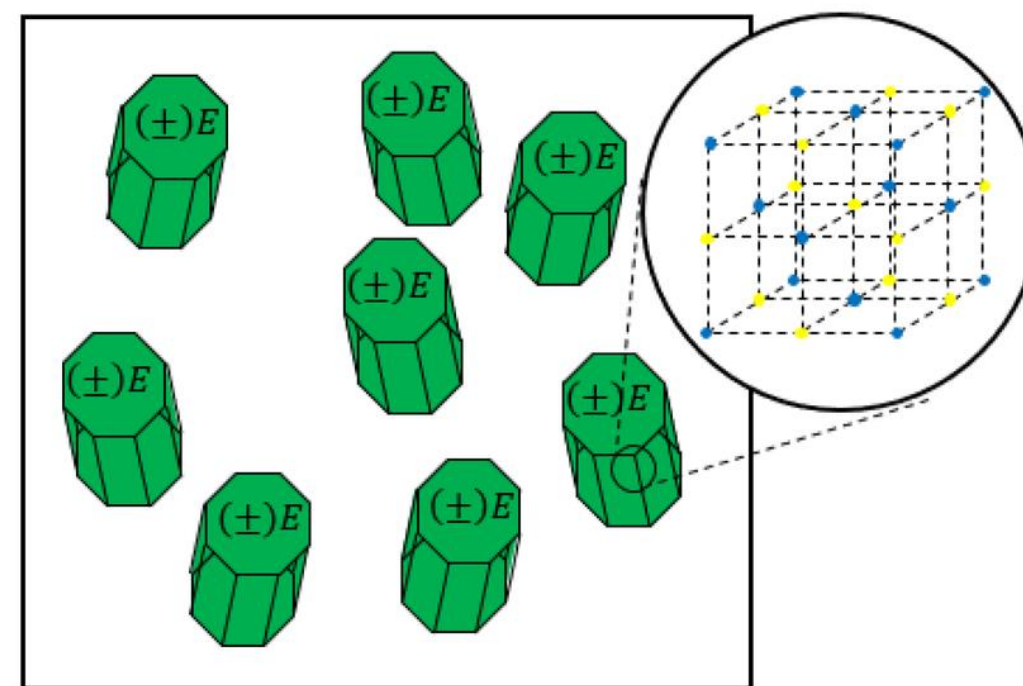
Conglomerate Crystals (a)



(+)E - (+)Enantiomer Crystals



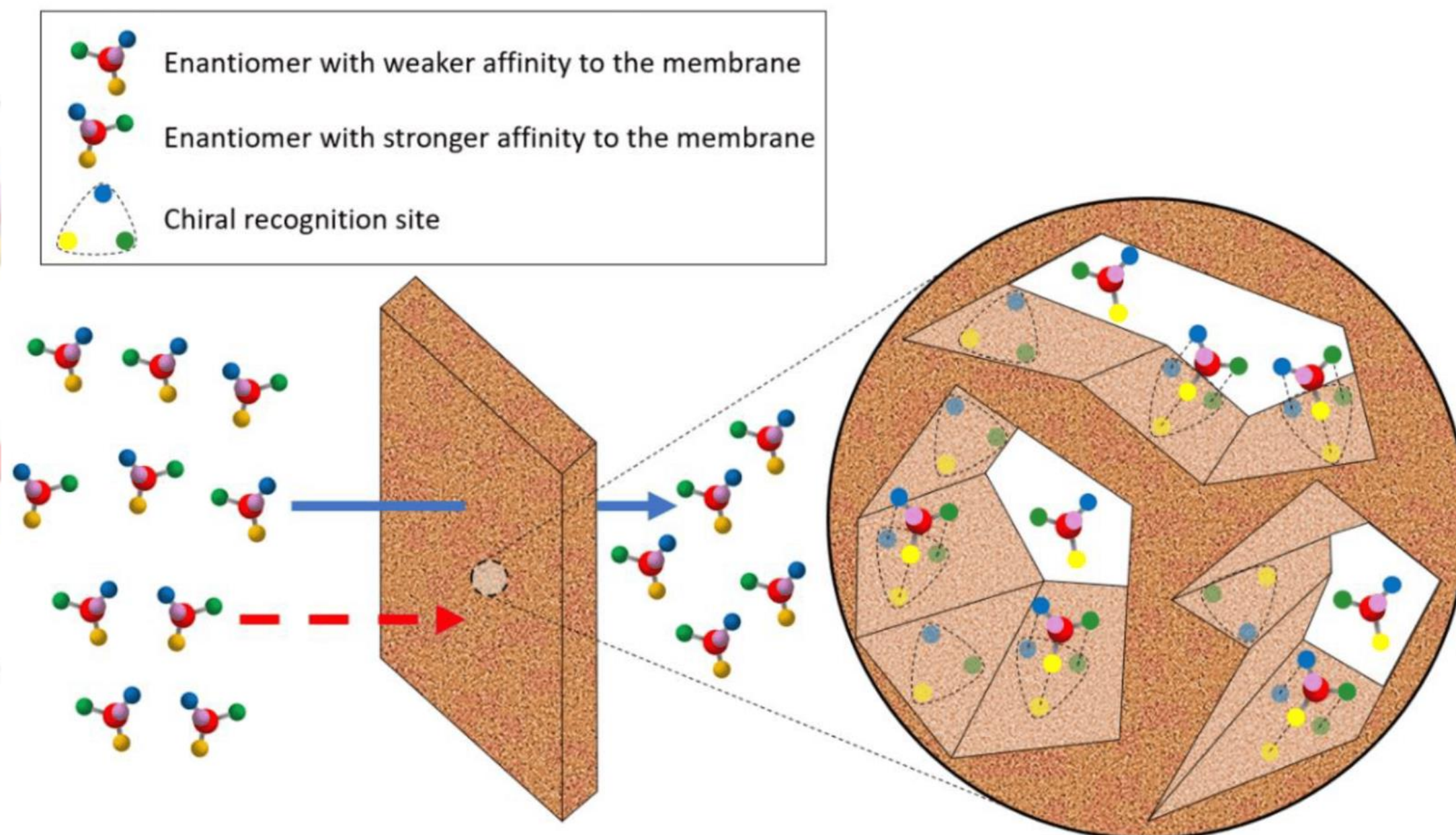
(-)E - (-)Enantiomer Crystals



Racemic Crystals (b)

Phenomenon of molecular dynamics based on many variables such as temperature, glass-forming ability of liquids.

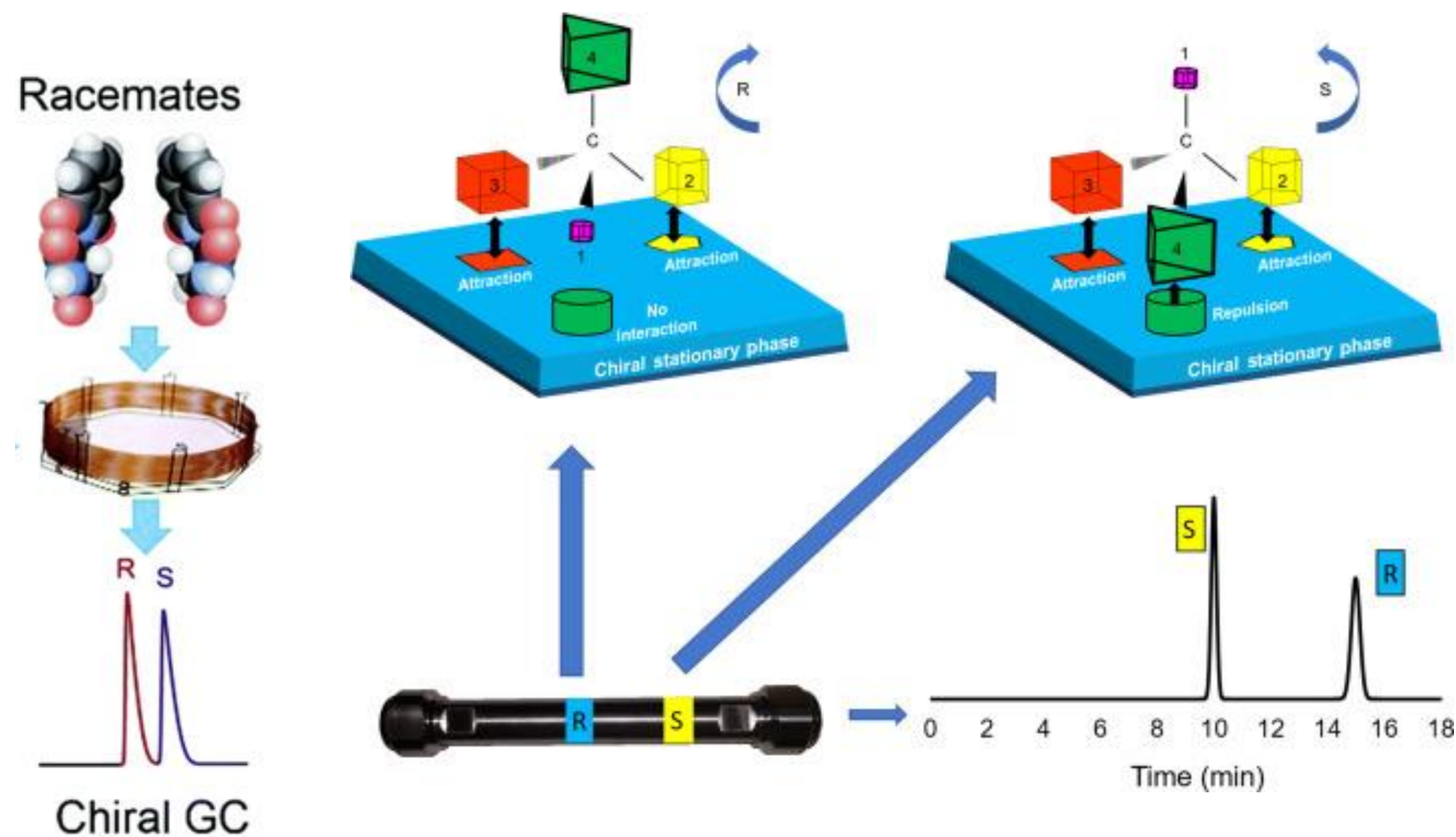
Enantio Resolution : Membrane



works as barriers with chiral recognition sites that selectively transport one of the enantiomers based on affinity between the enantiomer and chiral selector

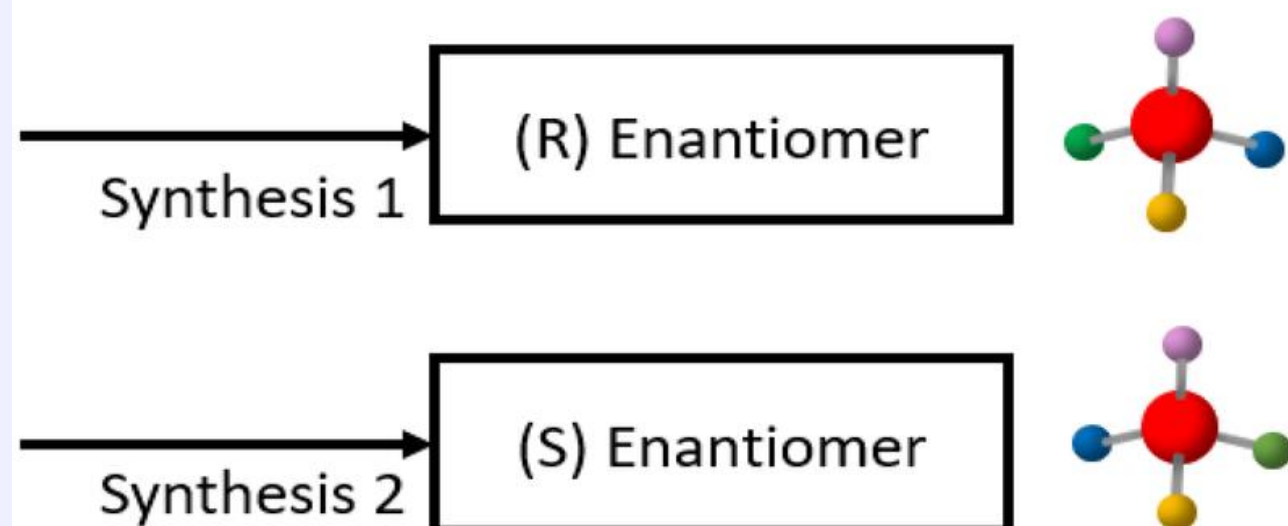
Enantio Resolution : Chromatography

Chromatographic methods have been the most effective for obtaining enantiomers with very high purity which could also applied with small amount samples for analytical purpose.



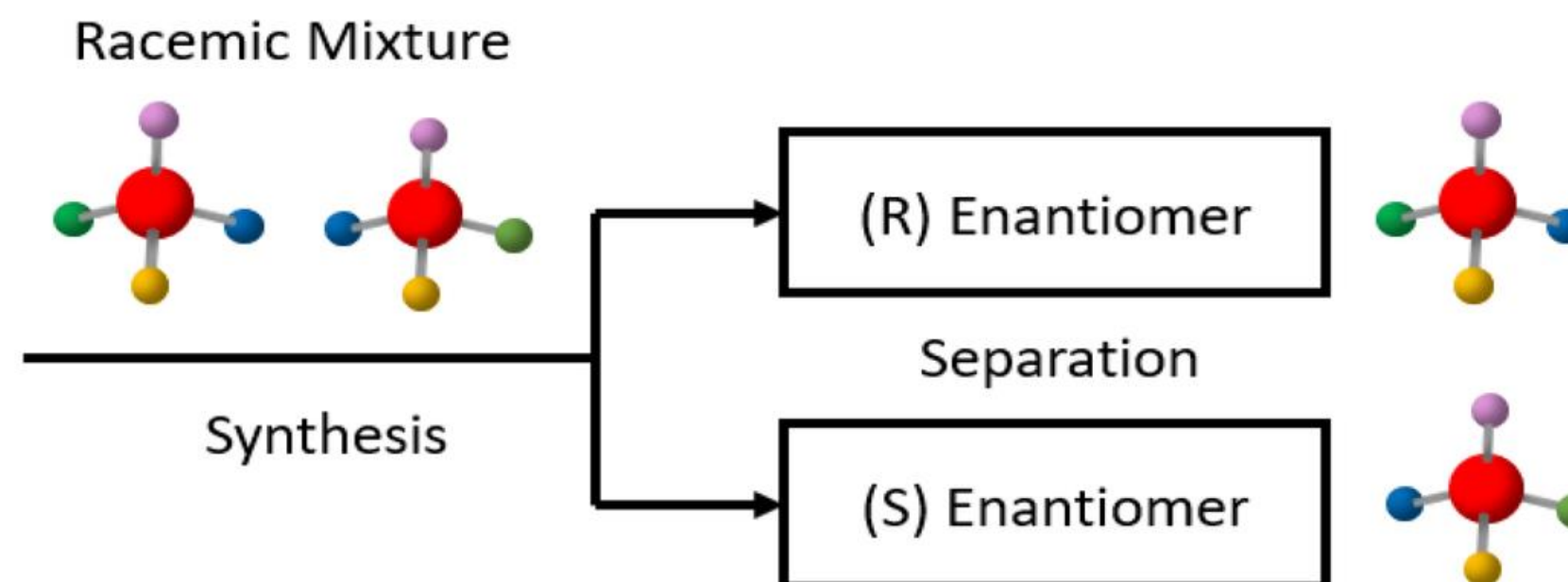
To obtain the pure form of chiral compounds...

Chiral Route Stereoselectivity



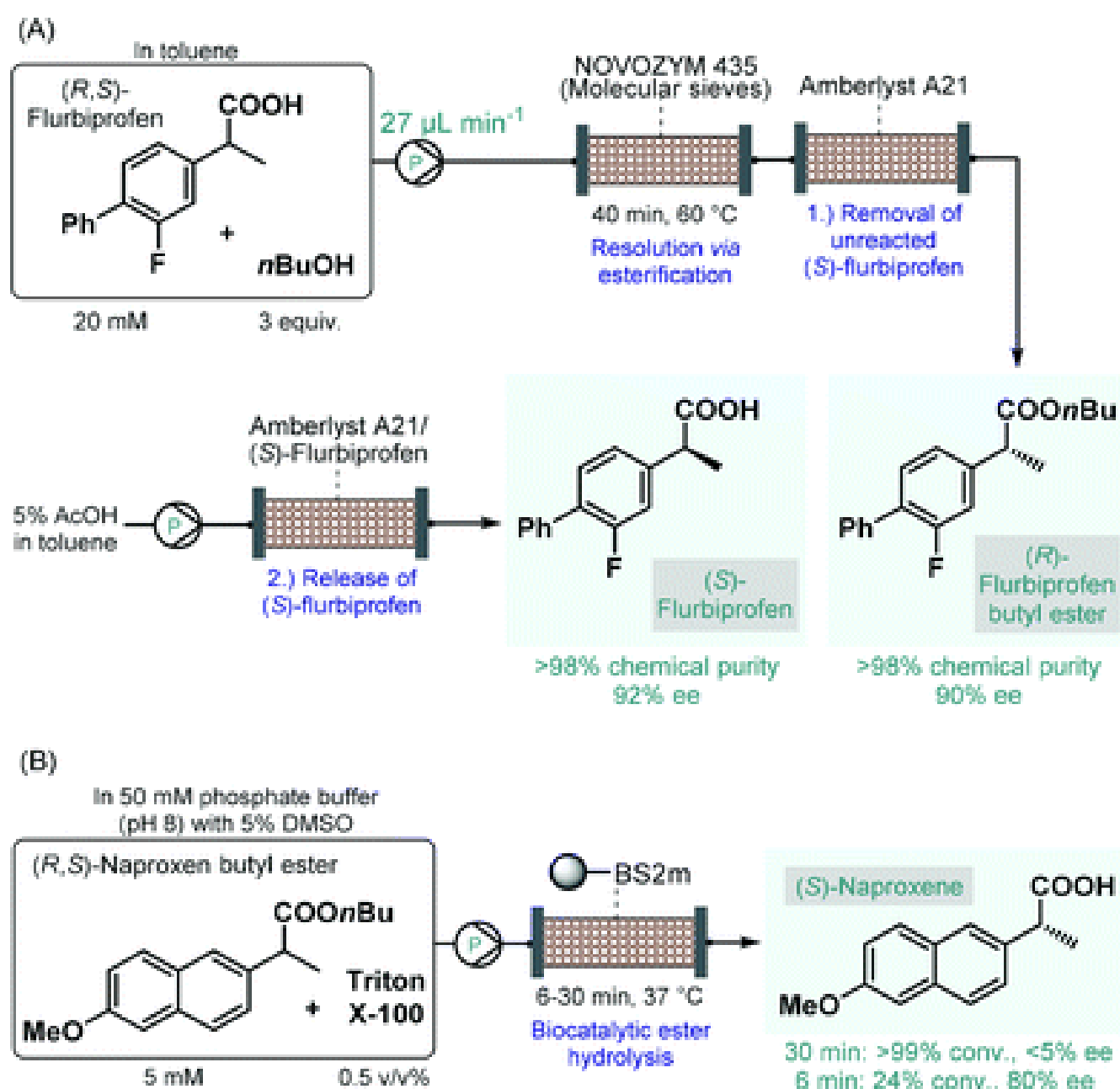
(a)

Racemic Route Racemic Synthesis



(b)

Chiral drug synthesis



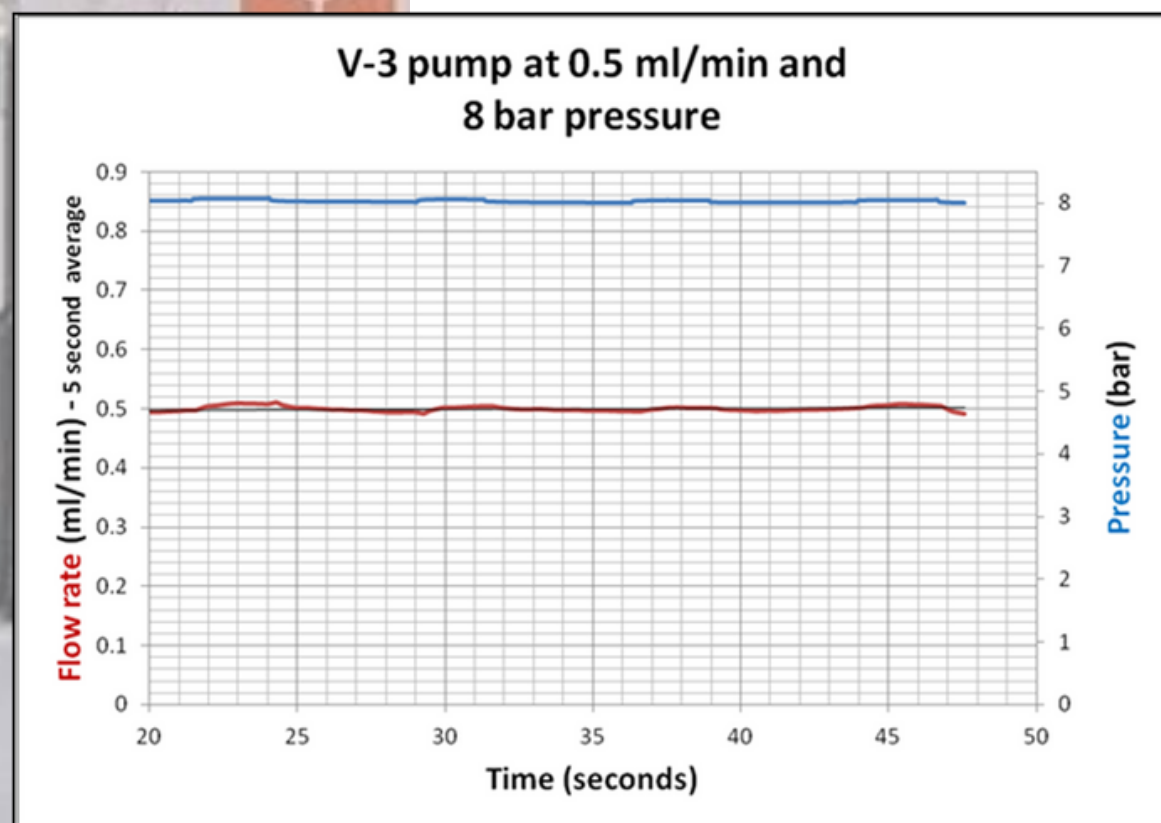
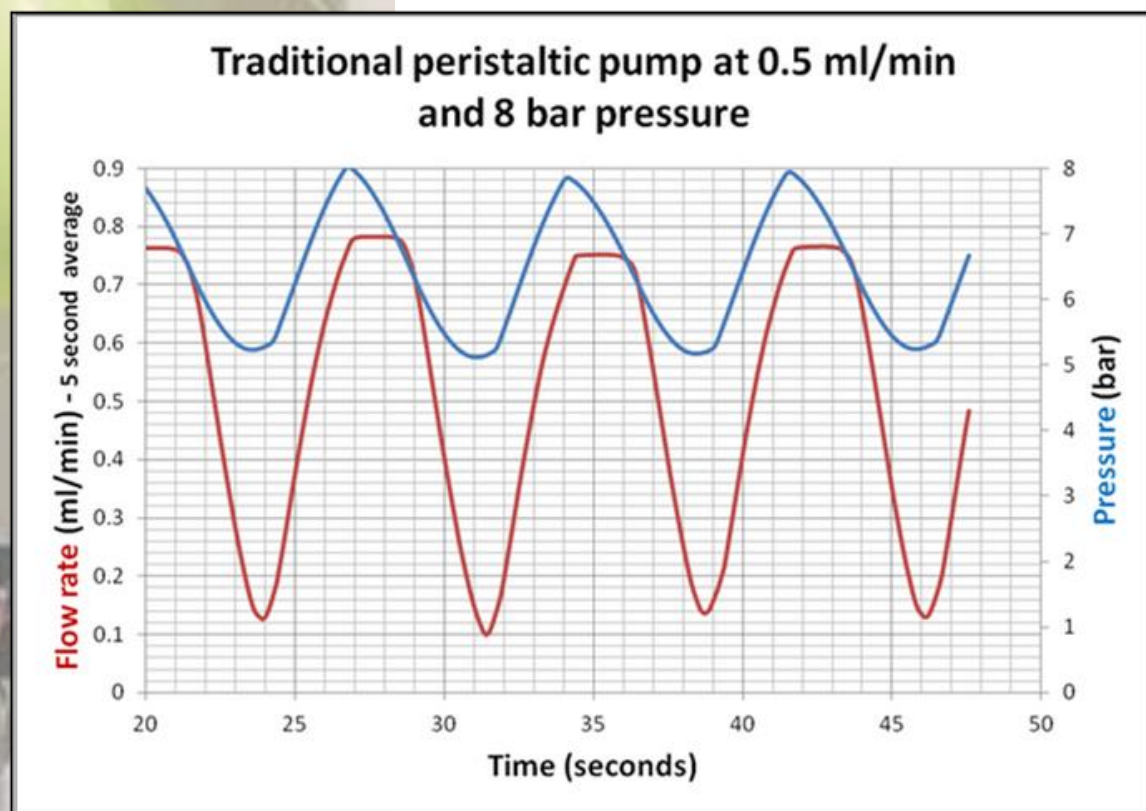
Batch Synthesis VS Flow Synthesis





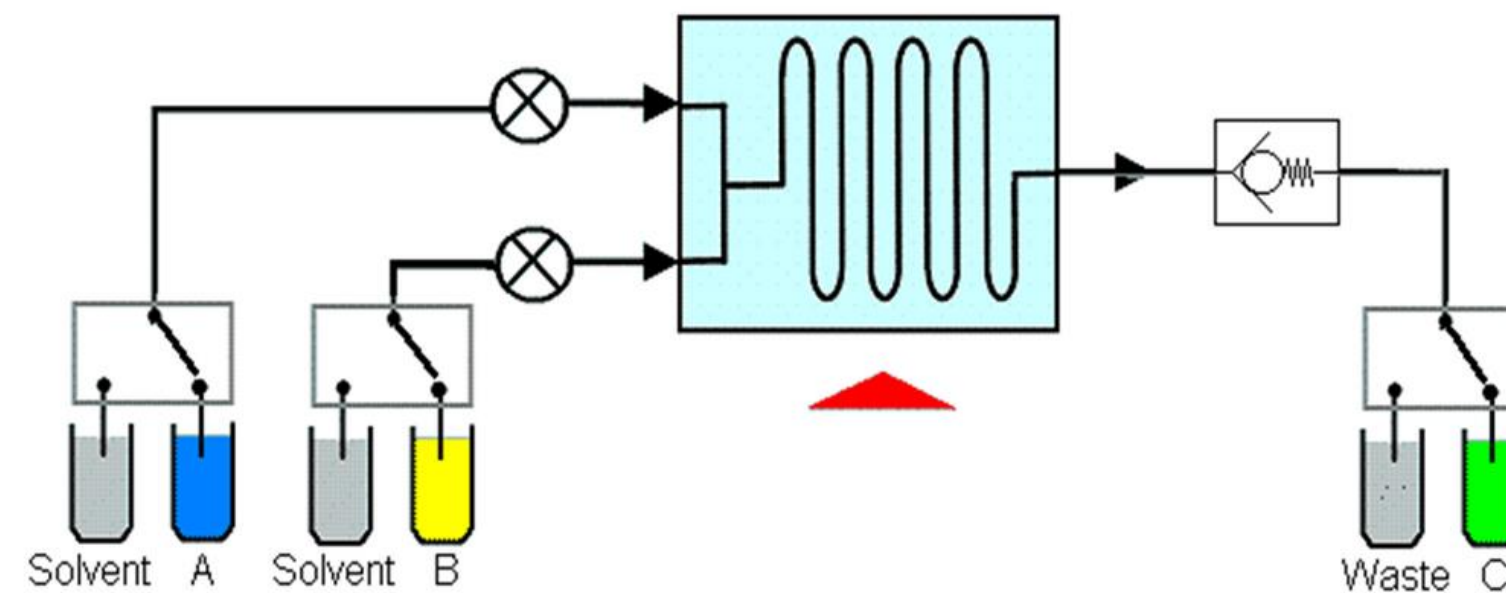
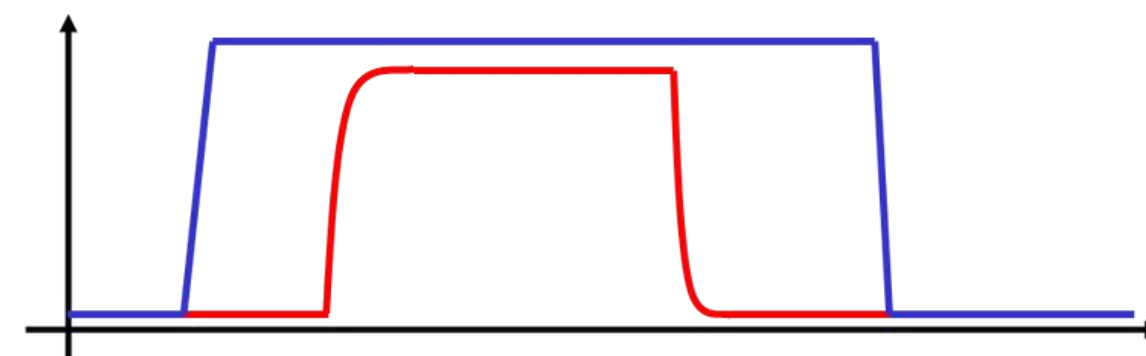
Batch Synthesis VS Flow Synthesis





Flow synthesis

Temperature
Pressure



Reduce the fluctuation of pressure and temperature in the reaction

Flow synthesis : Advantages over batch reaction

Reduce the fluctuation of pressure and temperature in the reaction

Require *less space*

Produce a *higher reaction yield*

Control the pressure and temperature in the *exothermic reaction*

Low back-mixing

No need to isolate the *reactive intermediate*

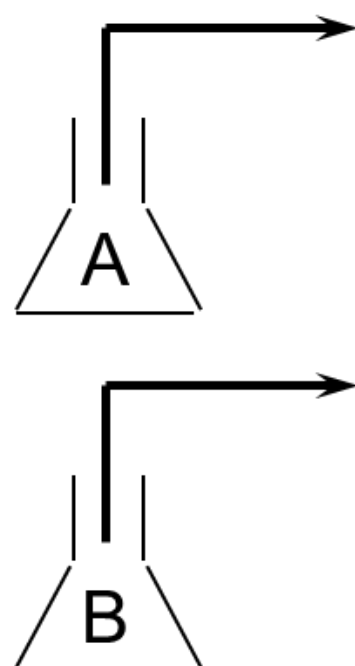


Flow synthesis : Variation synthesis scales

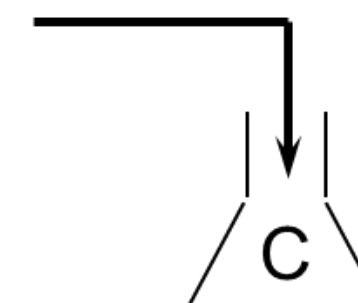
Flow principles can be applied to >14 orders of magnitude in scale, from earliest chemistry to late manufacturing

nano	micro	meso	kilo lab	pilot plant	manufacturing		
ng	→ μg	→ mg	→ g	→ kg	→ 10 kg	→ 100 kg	→ multi-ton

Scale translation?



Vapourtec R-Series



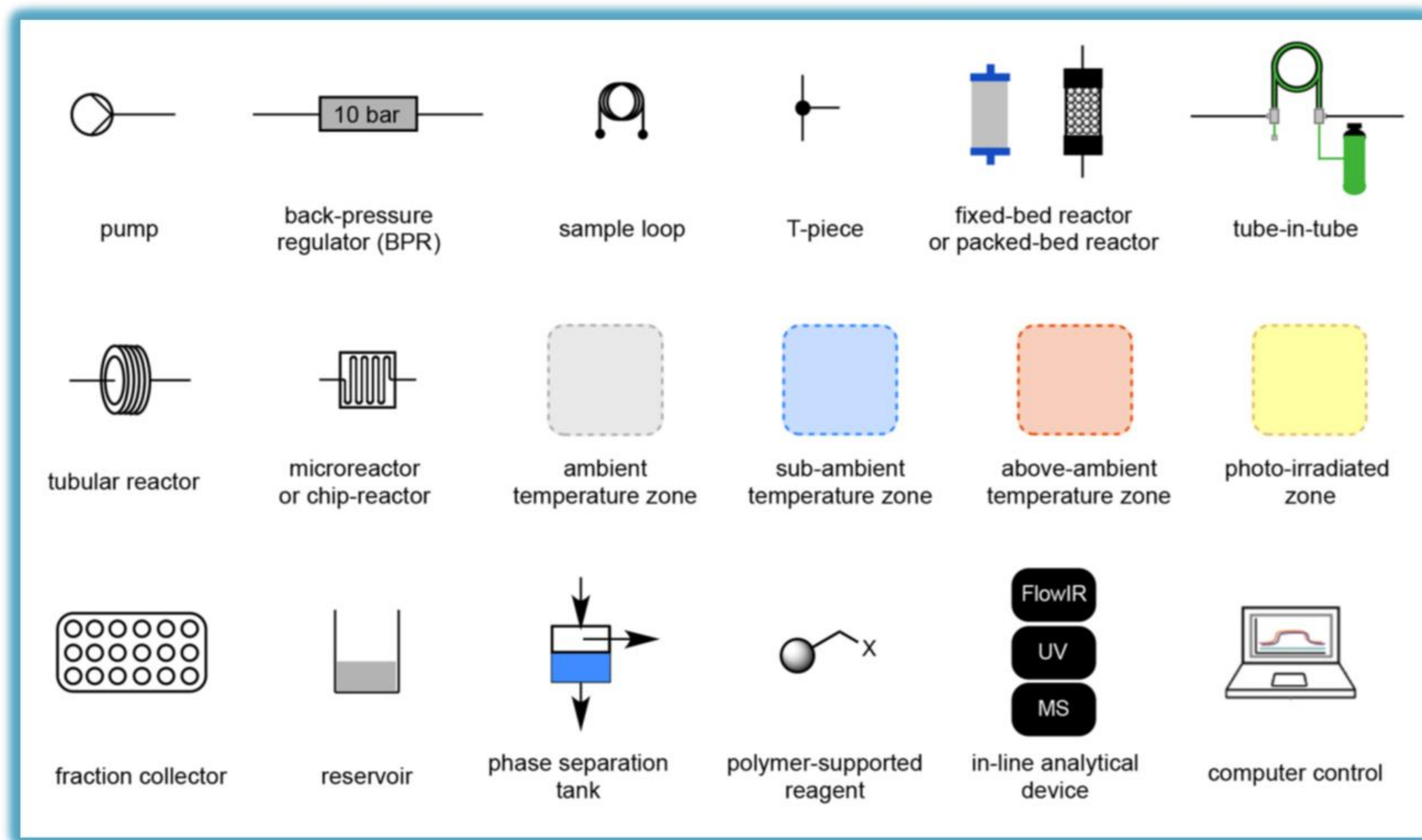
20 mg (convenience)
to 1000 g / day ("real chemistry")

Flow synthetic system component : Variation of reactors



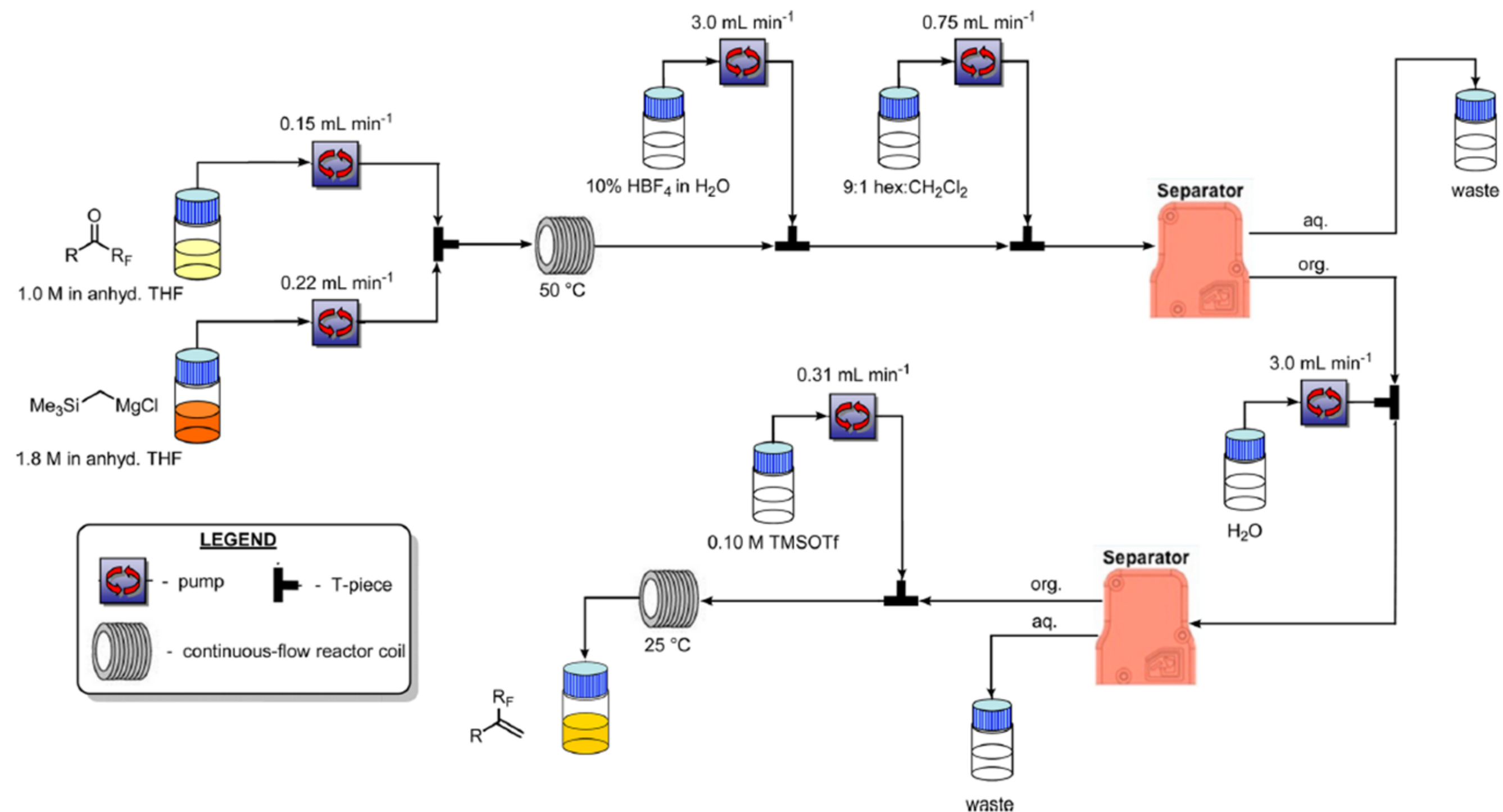


Flow synthesis : Key Components





Multistep, In-line Extraction and Solvent Switching

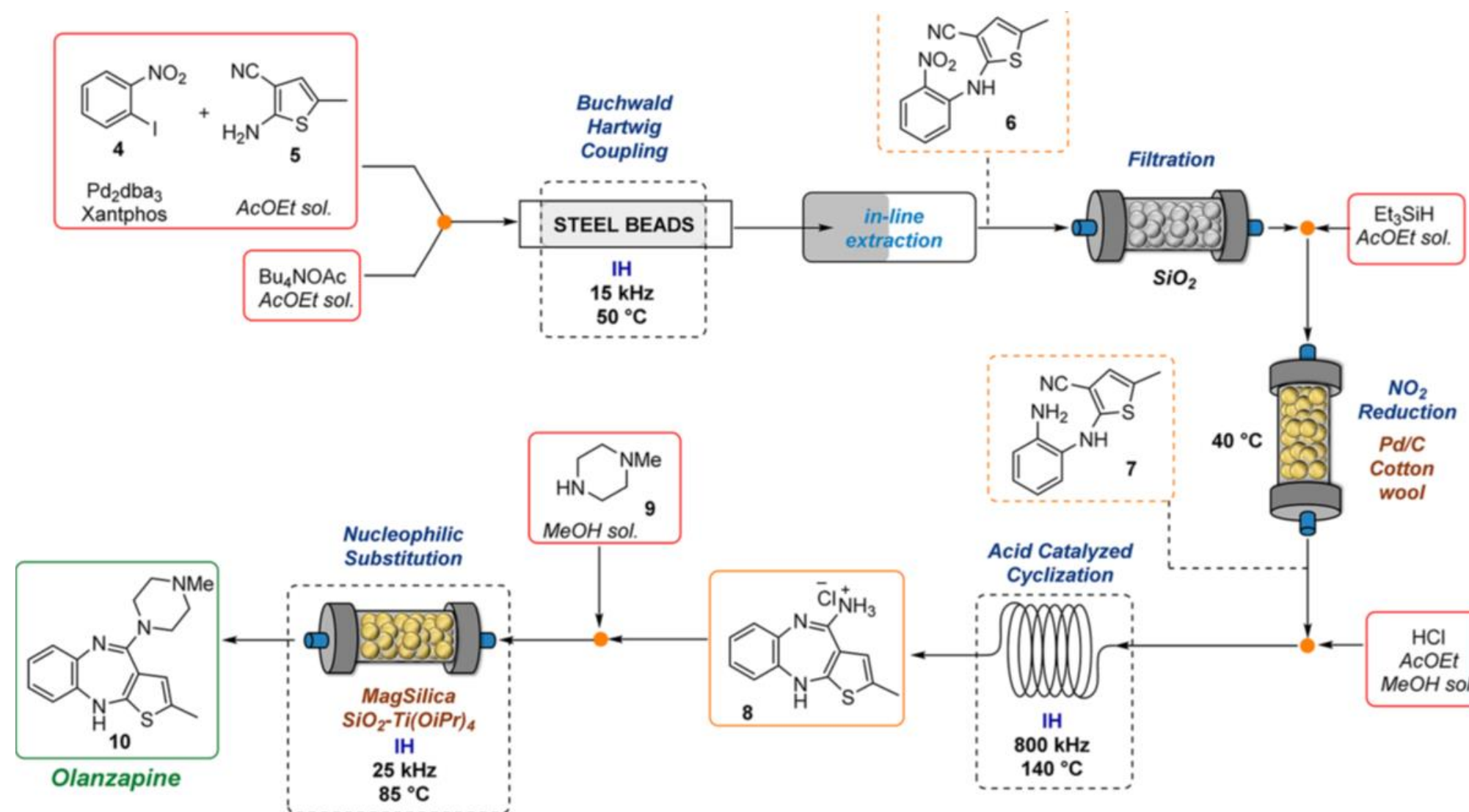




Flow synthesis : Application in Drug Synthesis

Synthesis of Olanzapine :

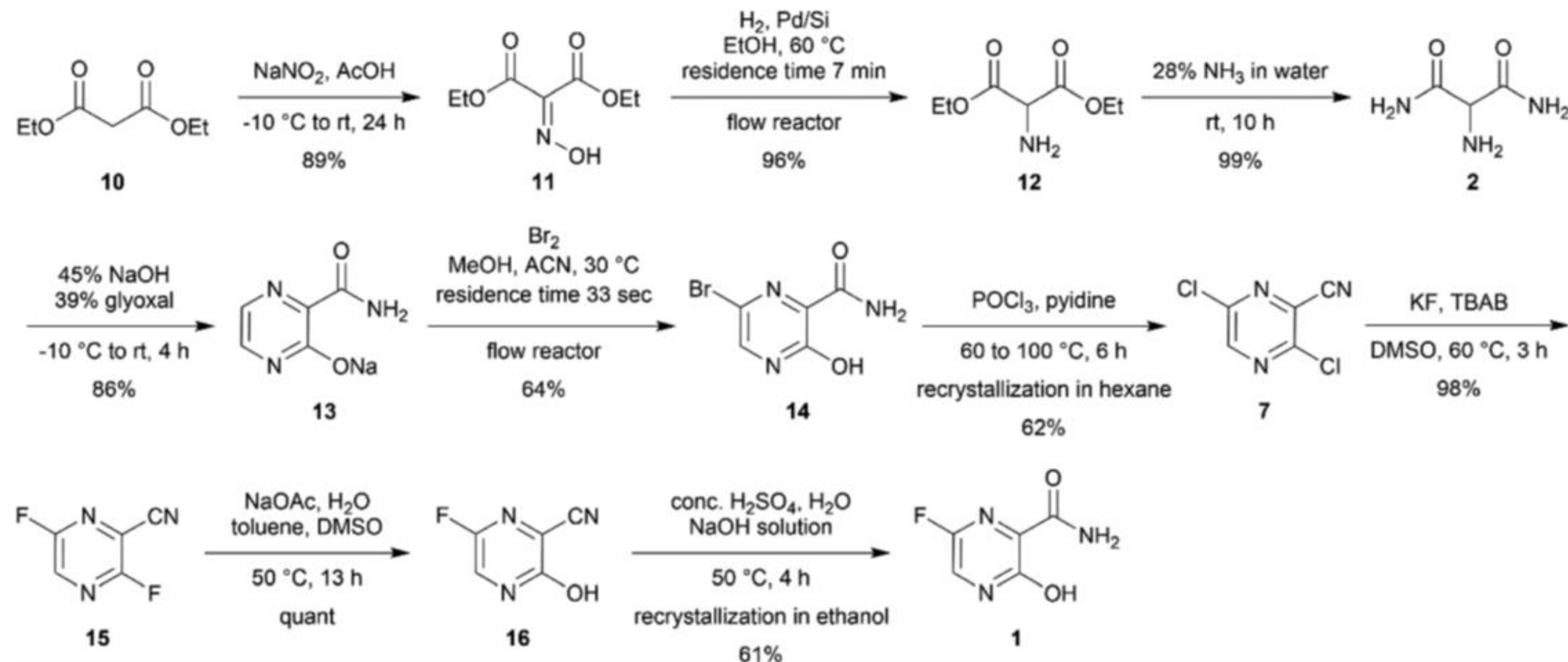
- Multistep synthesis of *API in flow*
- Crude mixture was passed through a silica cartridge in order to **remove Pd catalyst**
- Remarkably, the three step
- sequence did not require any solvent switch, and the **total reactor volume is about 8 mL only**.



Flow synthesis : Application in Drug Synthesis

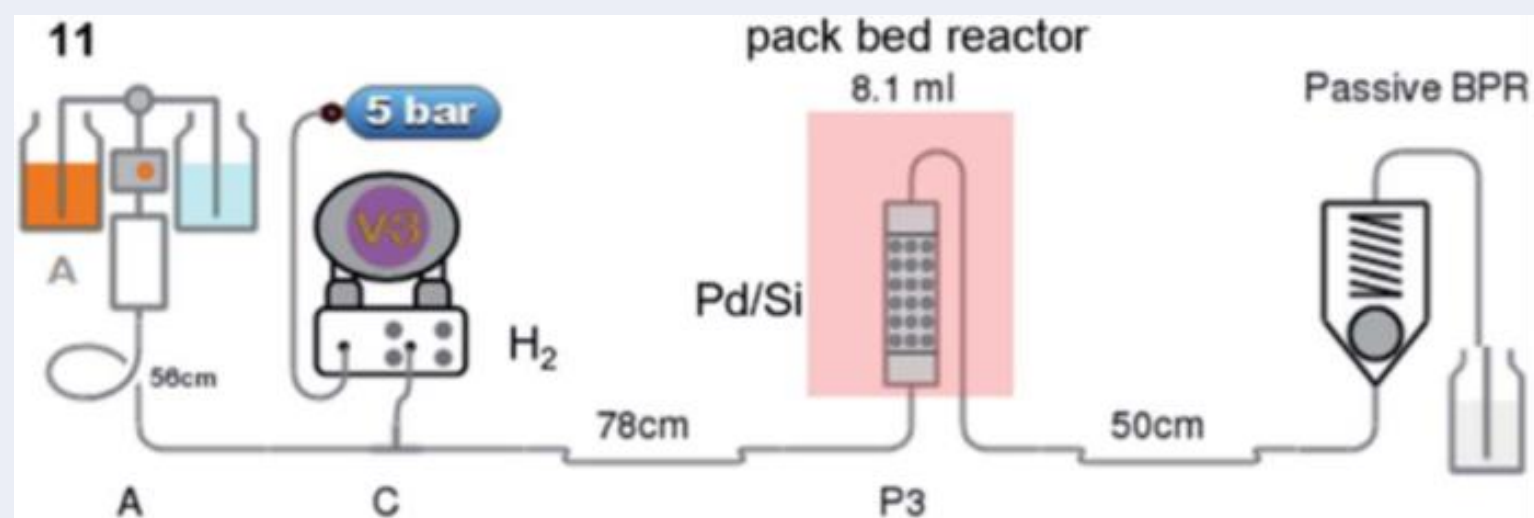
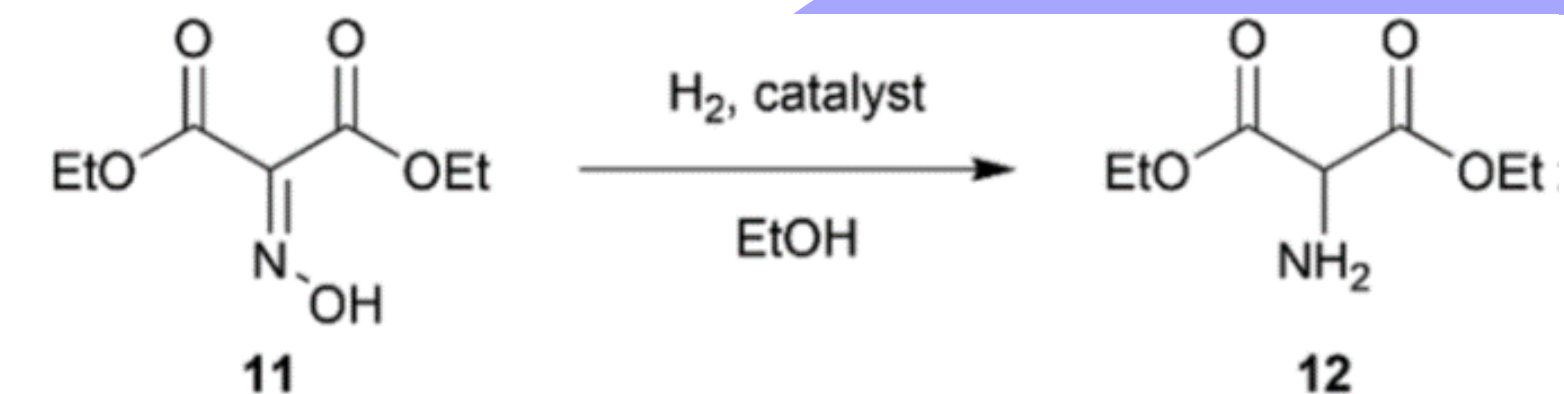
Synthesis of favipiravir :

- Using diethyl malonate as **cheap starting material**.
- Hydrogenation** and **bromination** steps were achieved by employing a continuous flow reactor.





Flow synthesis : Application in Drug Synthesis



Entry	Reagent	Catalyst	Time	Temp. (°C)	Conversion (%)
1 ^a	H ₂ (excess)	Pd/C, 5% wt	24 h	30	66
2	H ₂ (1 eq.)	Pd/Si	7 min	30	86
3	H ₂ (4 eq.)	Pd/Si	7 min	30	96
4	H ₂ (6 eq.)	Pd/Si	7 min	30	97
5	H ₂ (6 eq.)	Pd/Si	7 min	60	100 ^b
6	H ₂ (6 eq.)	Pd/Si	14 min	30	94

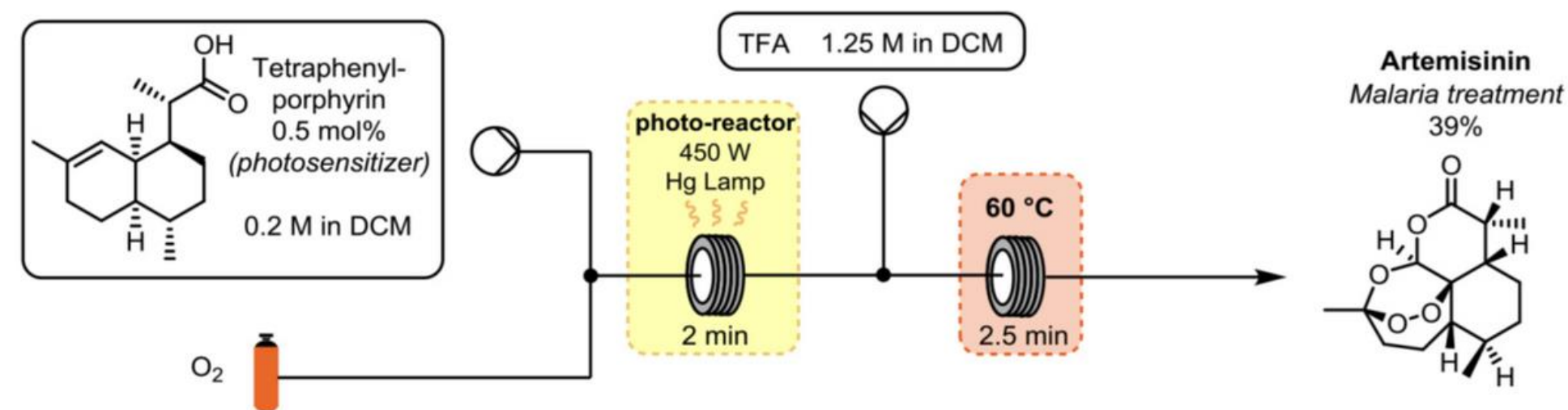
^a In a batch process. ^b Isolation yield ~80% or able to use without further purification.



Flow synthesis : Application in Drug Synthesis

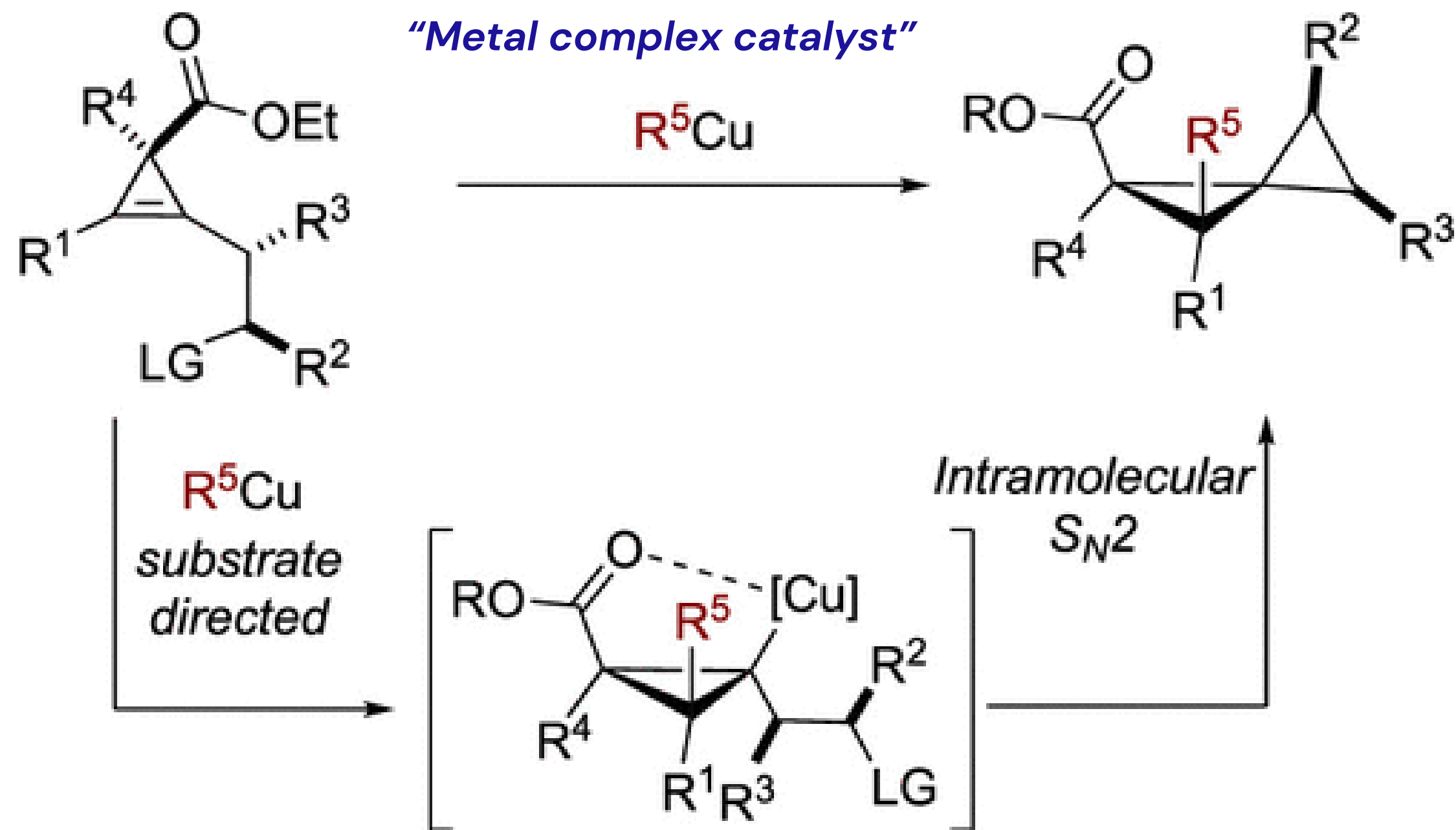
photochemical synthesis artemisinin :

photochemical singlet oxygenene reaction
where the resultant peroxy-ene species then undergoes Hock cleavage in the presence of trifluoroacetic acid





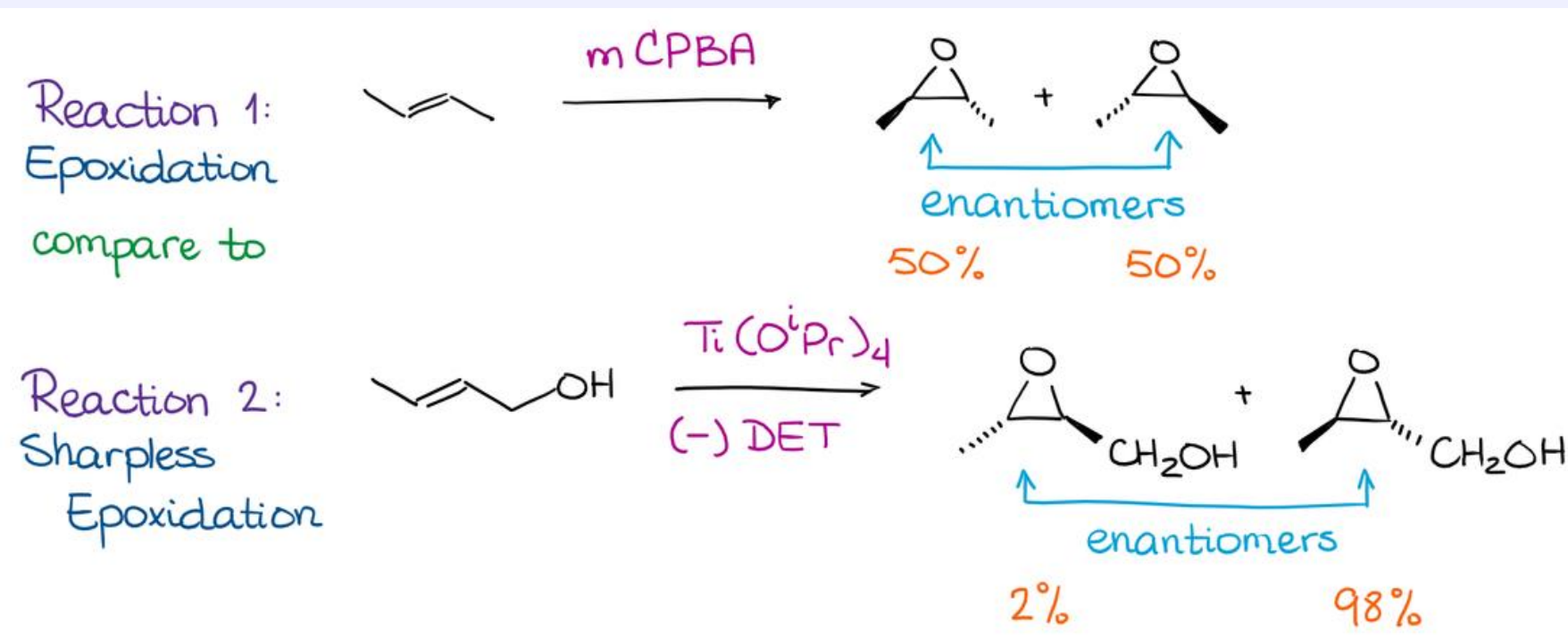
Flow synthesis : Application in *Stereospecific Drug Synthesis*



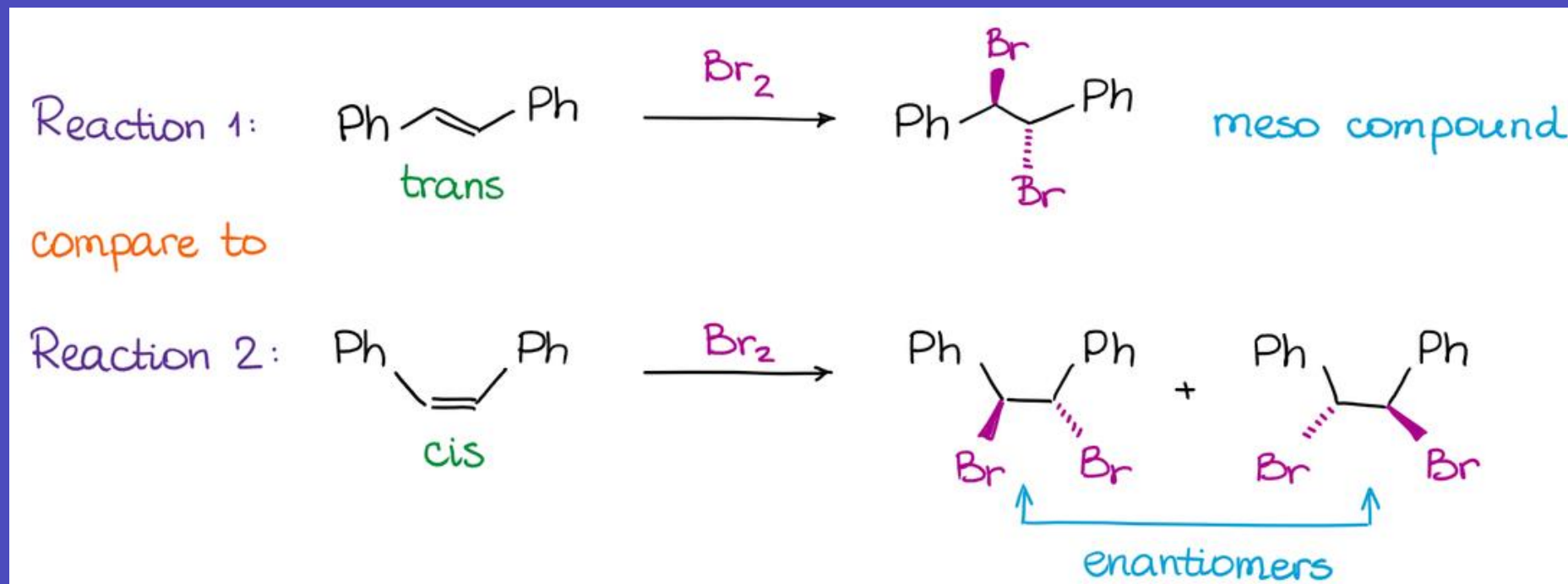
Stereoselective VS Stereospecific

Depends on :

- *mechanism*
- *starting materials*
- *catalyst*



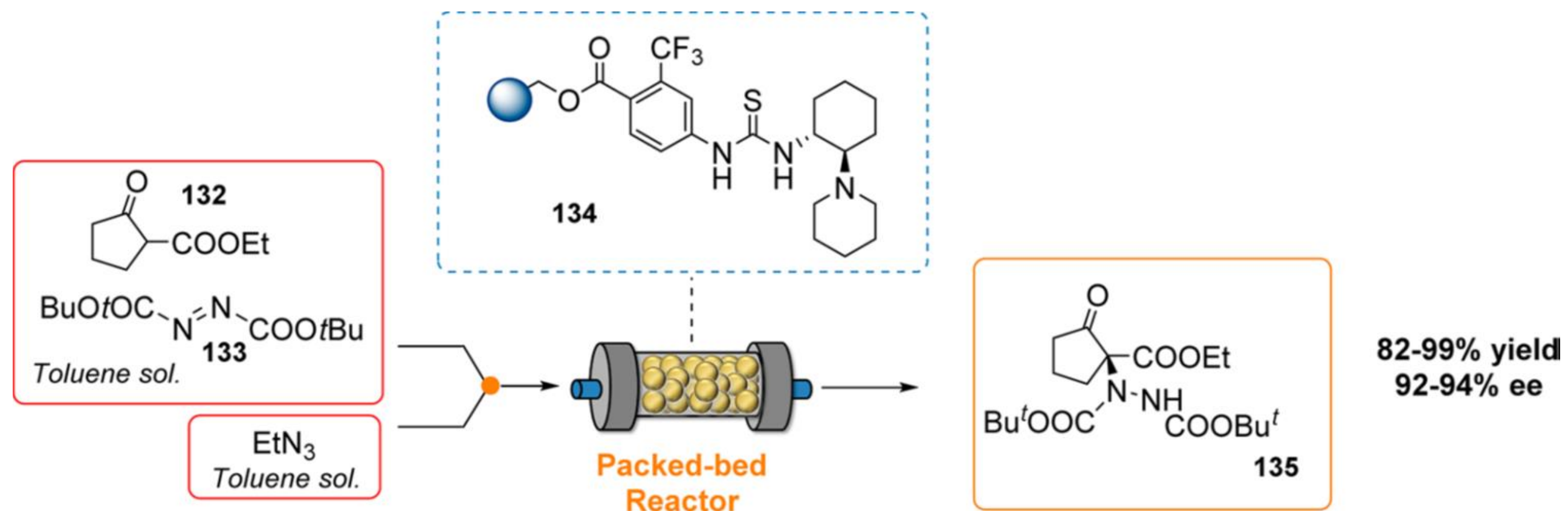
The reaction that can give different two isomers but one of those is *major* isomer.



Flow synthesis : Application in *Stereospecific Drug Synthesis*

Stereoselective α -Aminations :

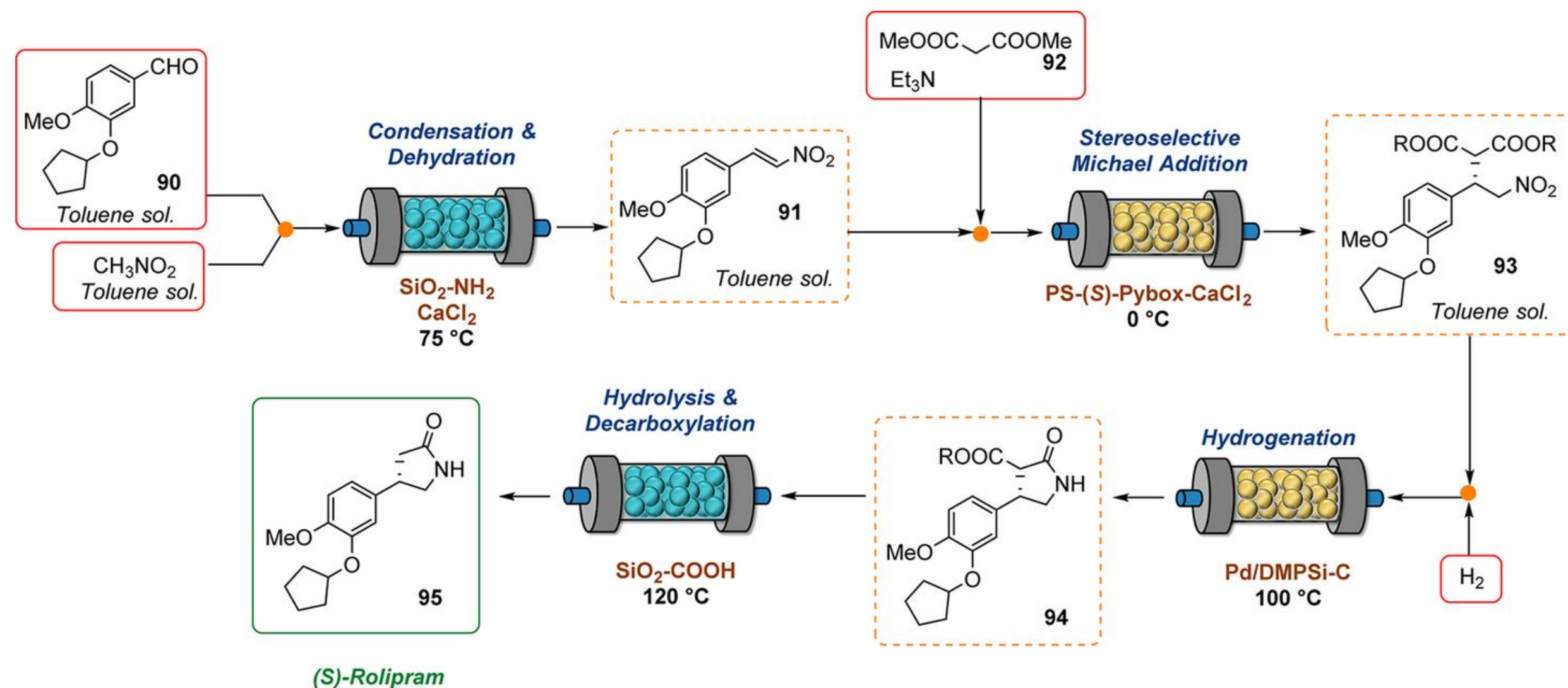
The reaction was tested under continuous flow conditions in a packed-bed column with a pump feeding the reagents for a residence time of 21 min.



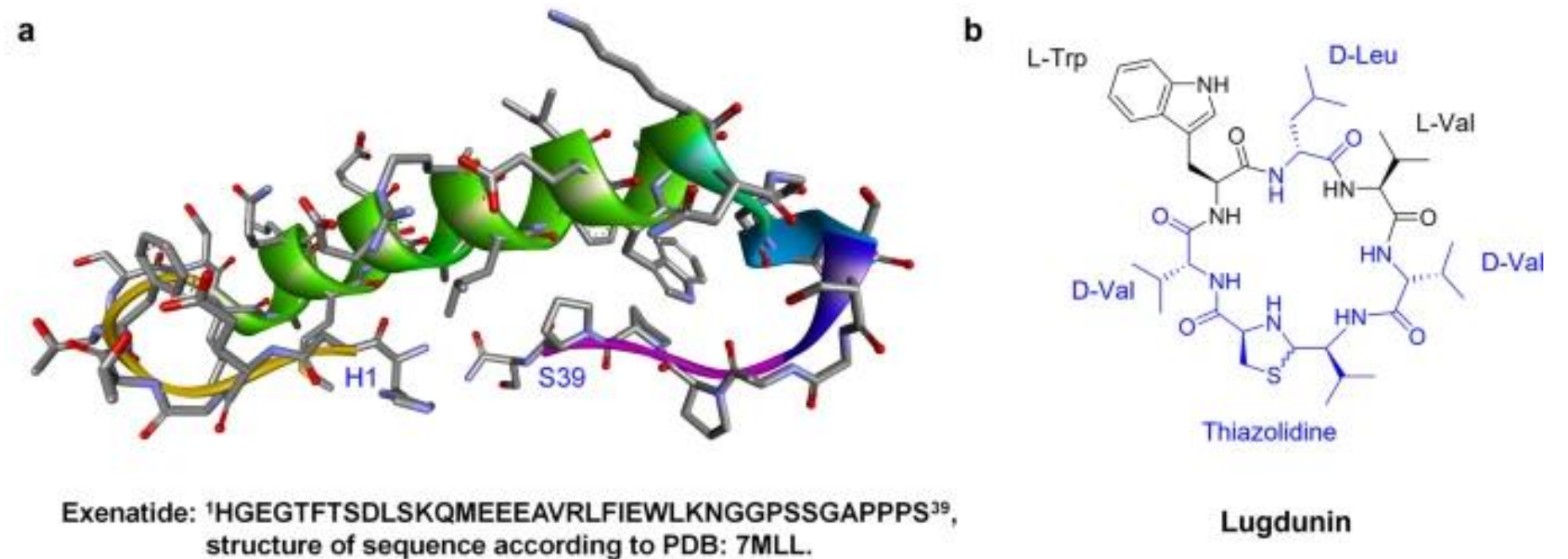
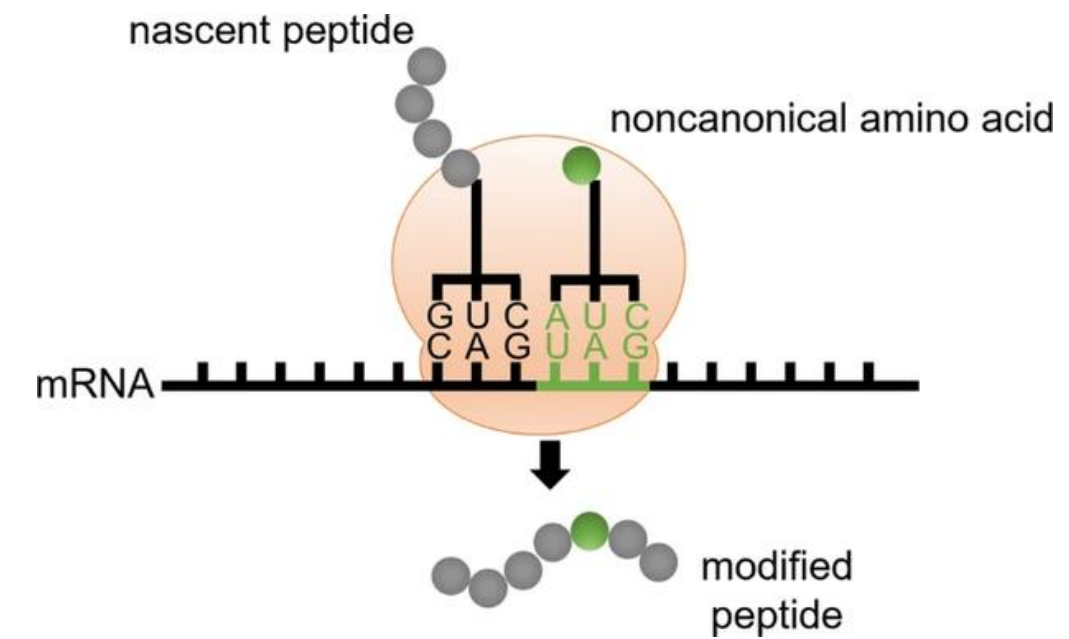
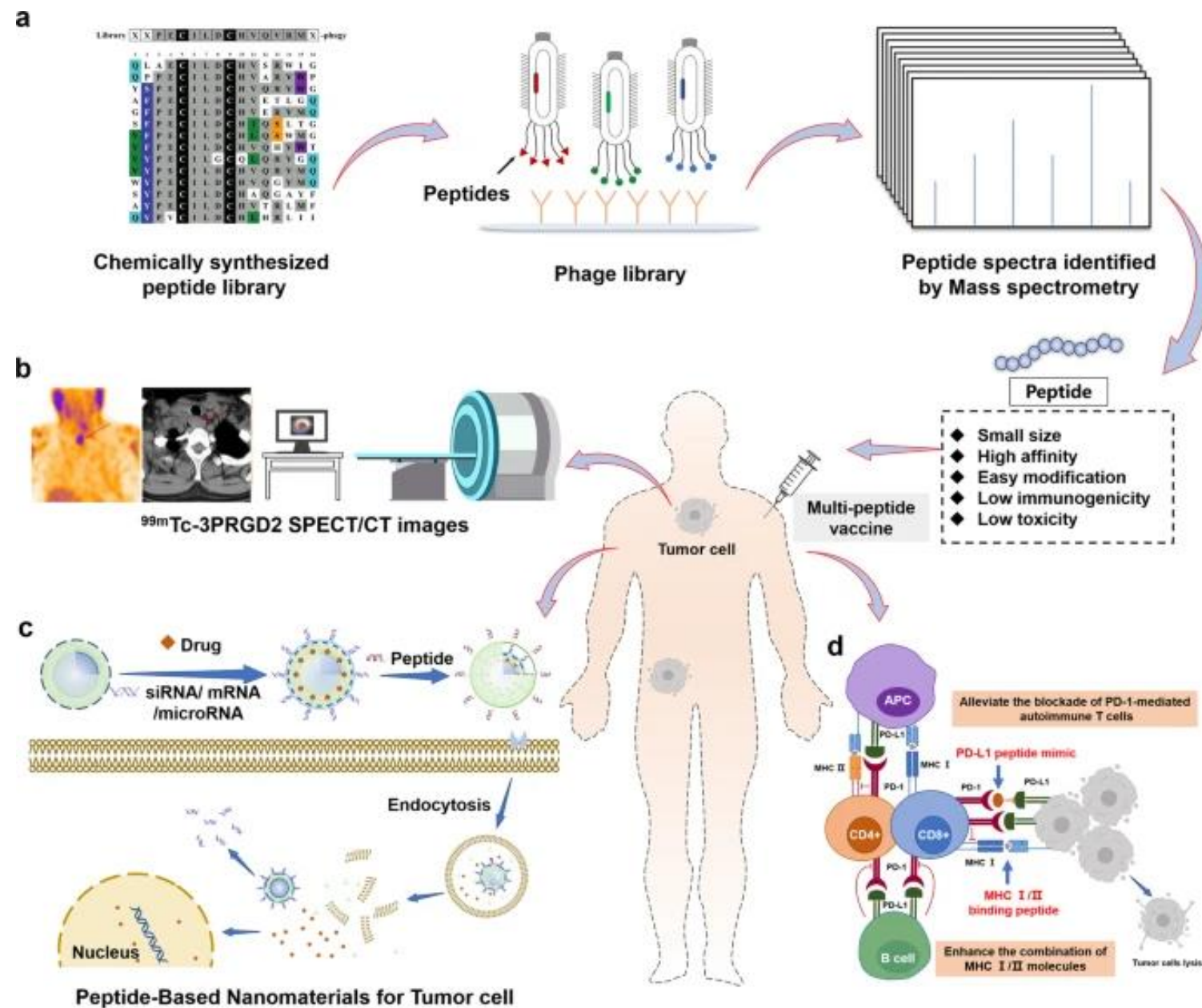
Flow synthesis : Application in *Stereospecific Drug Synthesis*

Synthesis of (S)-Rolipram

Continuous flow multistep synthesis of (S)-rolipram 95 by using reactors containing solid supported catalyst and reagents, without requiring any intermediate operation

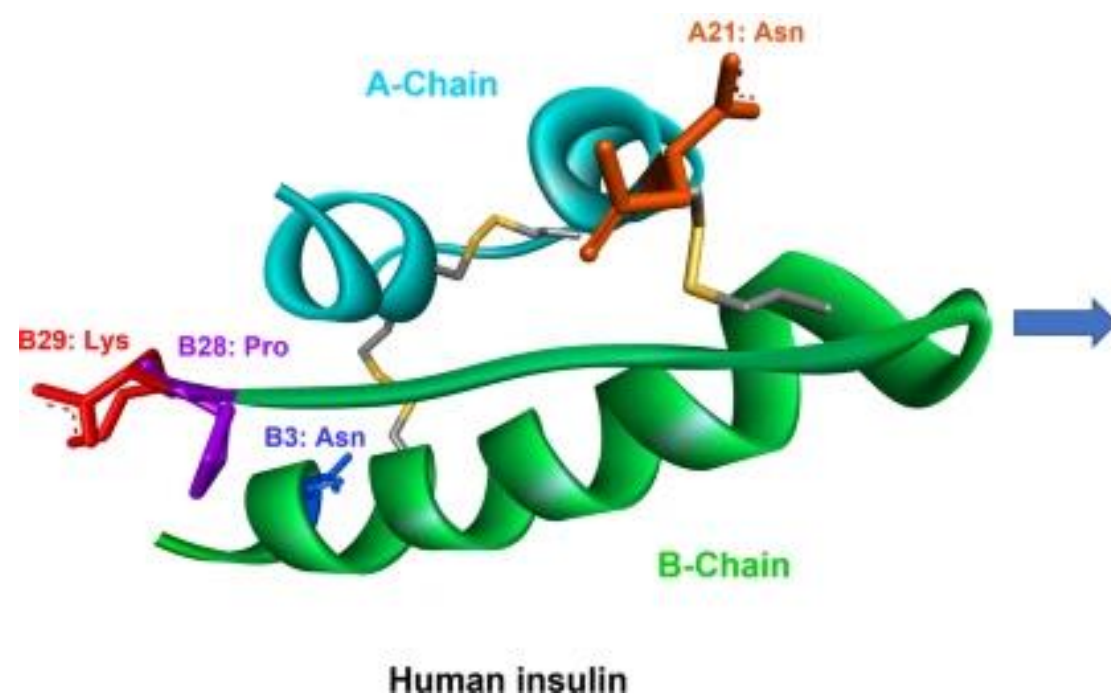


Flow synthesis : *Therapeutic peptide Drugs*

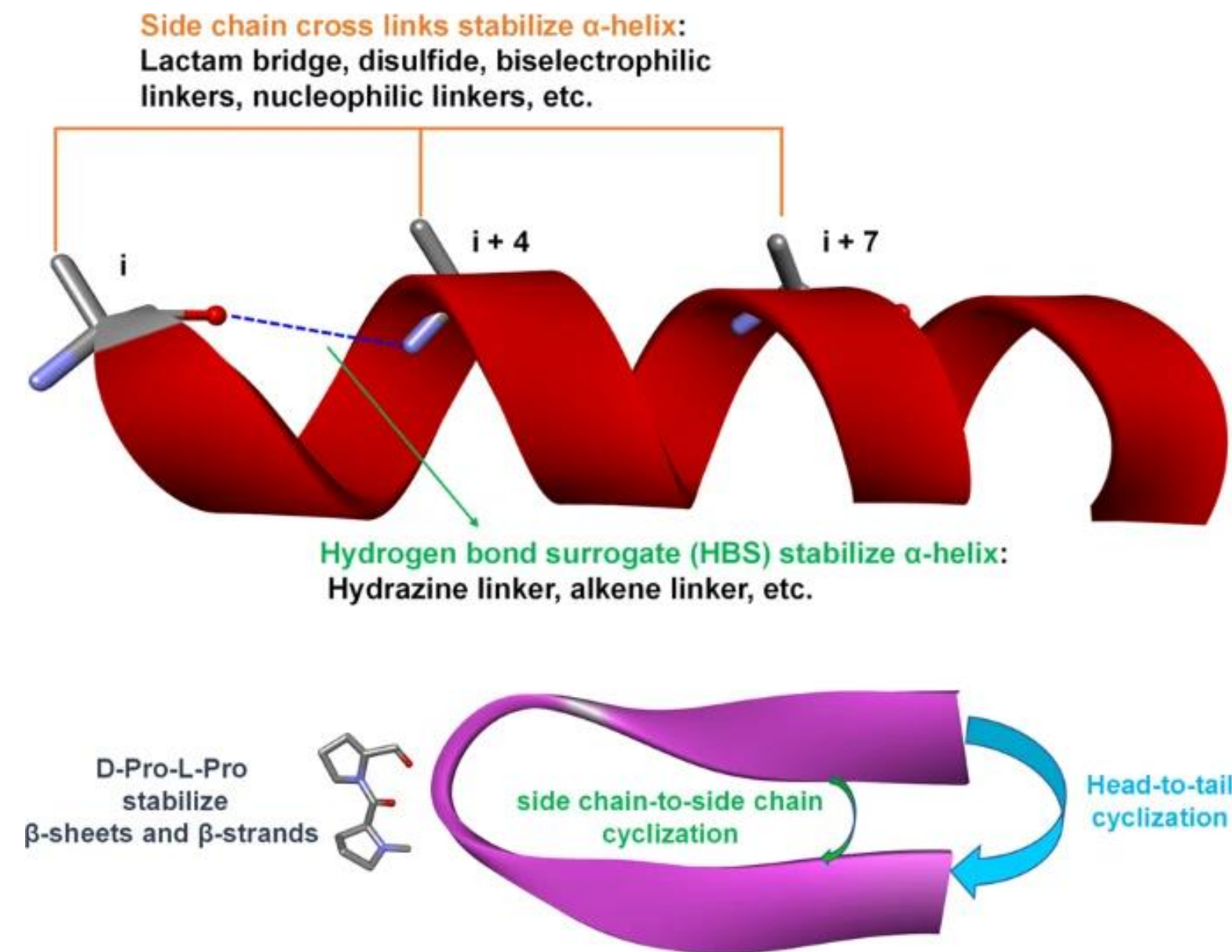


Flow synthesis : *Therapeutic peptide Drugs*

Human Insulin derived Drug



Insulin derived drugs	Sequence Modification
Short-acting insulin	Insulin lispro: B28: Lys B29: Pro
	Insulin aspart: B28: Asp
	Insulin glulisine: B3: Lys B29: Glu
Long-acting insulin	Insulin glargine: A21: Gly; addition of two Arg to the C-terminus of the B-chain(B31 and B32)
	Insulin detemir: B29: Lys linked with myristic acid
	Insulin degludec: B29: Lys linked with hexadecanedioic acid



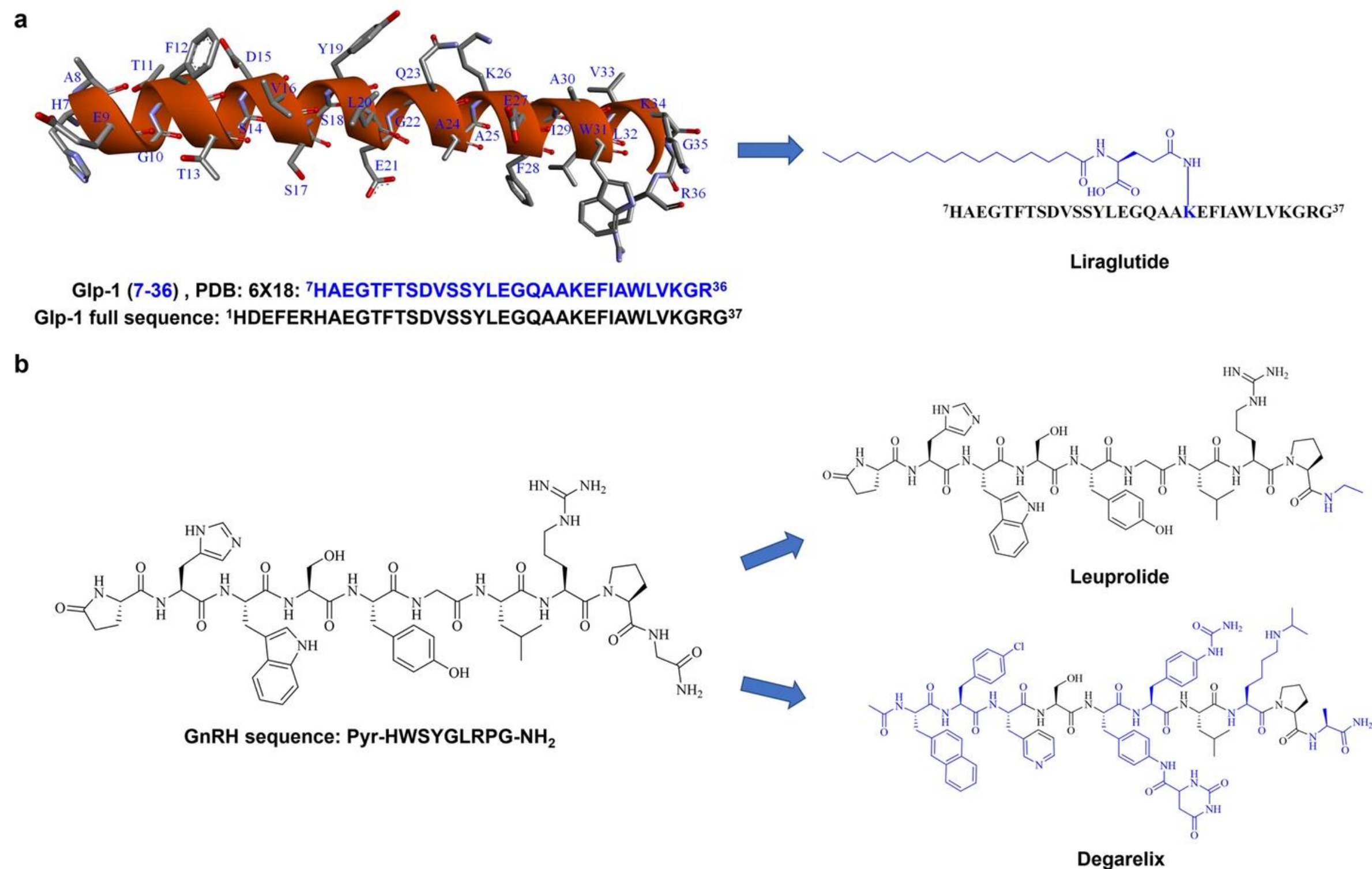
Strategies of peptide cyclization and stabilization

Flow synthesis : *Therapeutic peptide Drugs*

Sequences and structures of natural hormones GLP-1 and GnRH and their peptidomimetic drugs

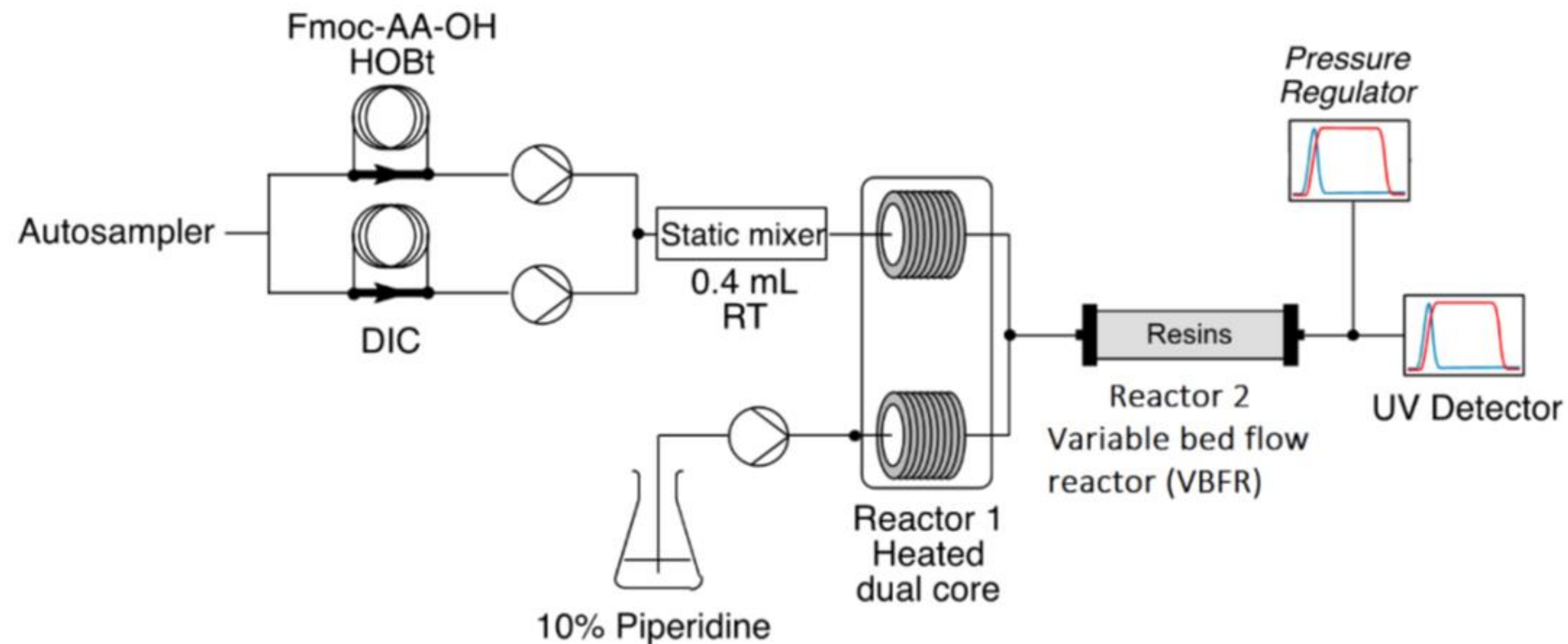
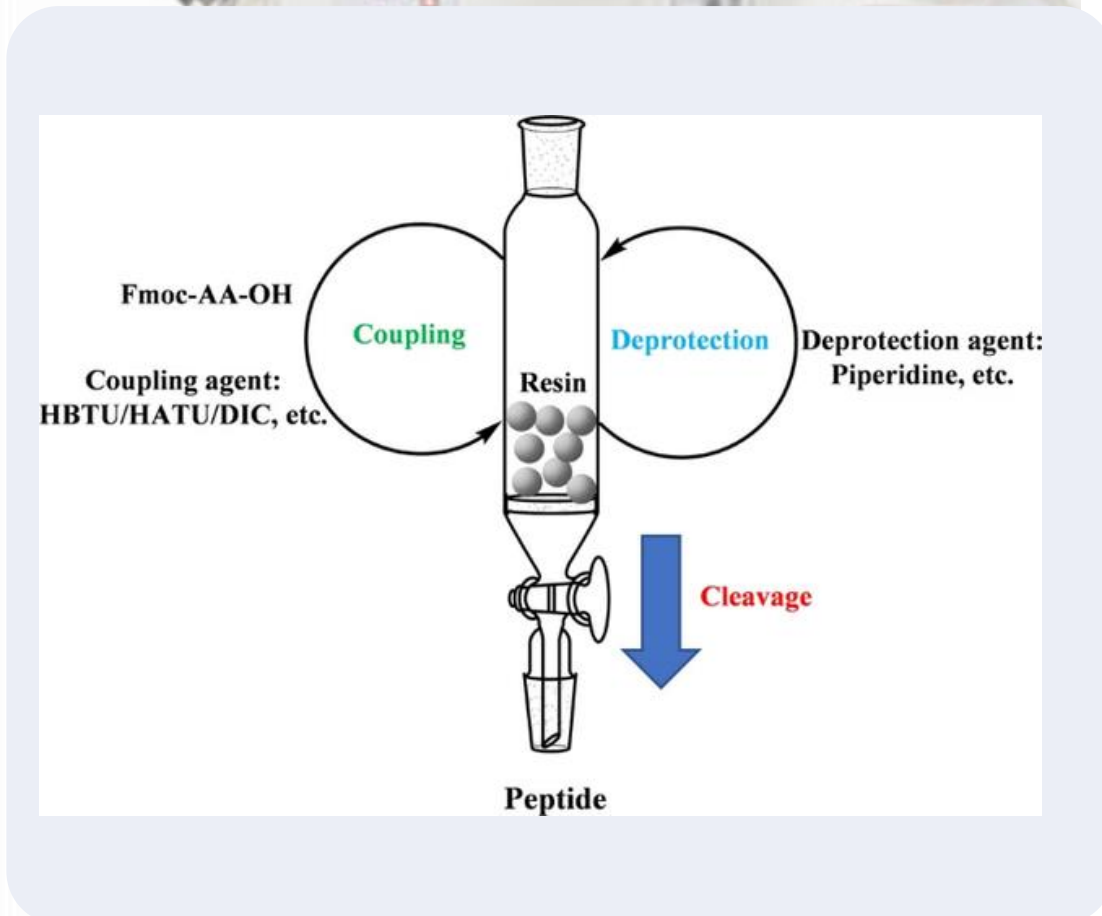
a) Liraglutide is a GLP-1 derived peptide drug, modified on 26th residue (K) of its natural sequence.

b) Leuprolide and degarelix are modified from the natural sequence of GnRH





Flow synthesis : *Solid Phase Peptide Synthesis*

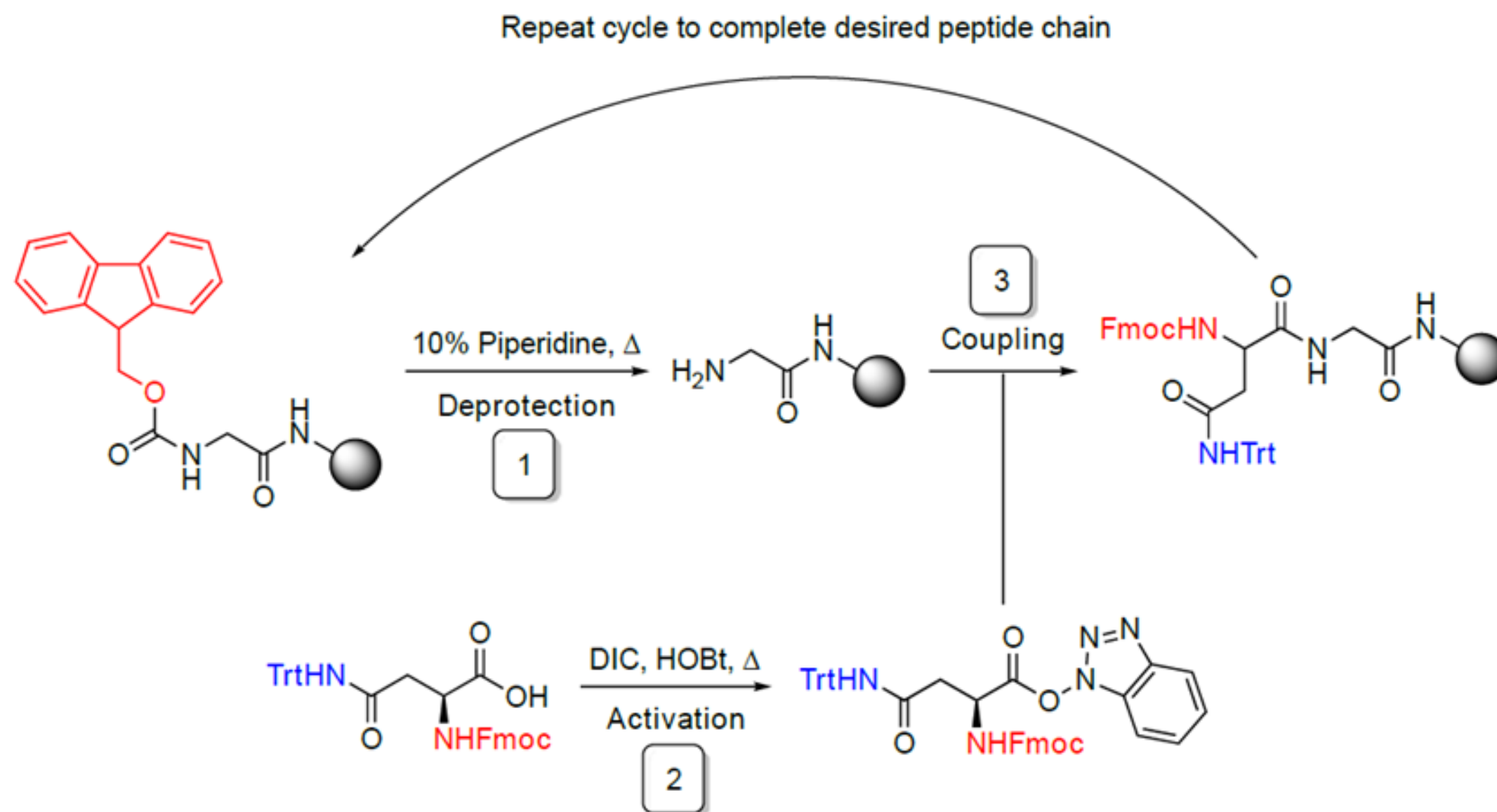


Solid Phase Peptide Synthesis:

the *Fmoc/tBu* solid phase peptide synthesis (SPPS) has become the standard method of synthesizing a range of peptides.

In-line UV detection, resin swelling and other reaction data can be directly monitored via the Vapourtec R-series software.

Flow synthesis : *Solid Phase Peptide Synthesis*



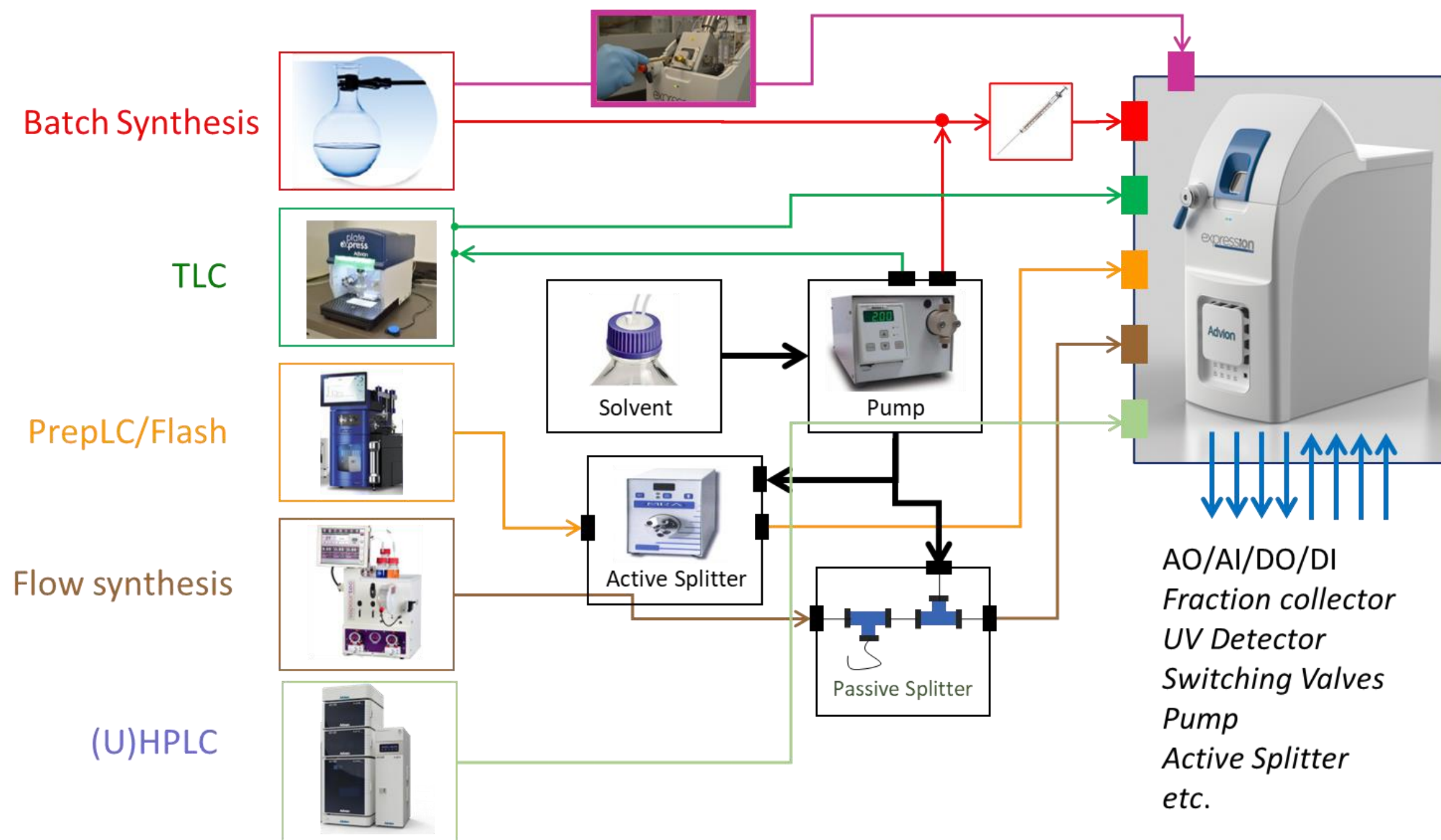
Flow synthesis : *Solid Phase Peptide Synthesis*

Solid Phase Peptide Synthesis: Pilot scale

Vapourtec has unveiled its Peptide-Pilot™, a unique, 'game changing' solid phase peptide synthesizer (SPPS) that reduces the drug development cycle time for significant quantities of target peptides from weeks to less than a day when compared to traditional, room temperature batch methods.



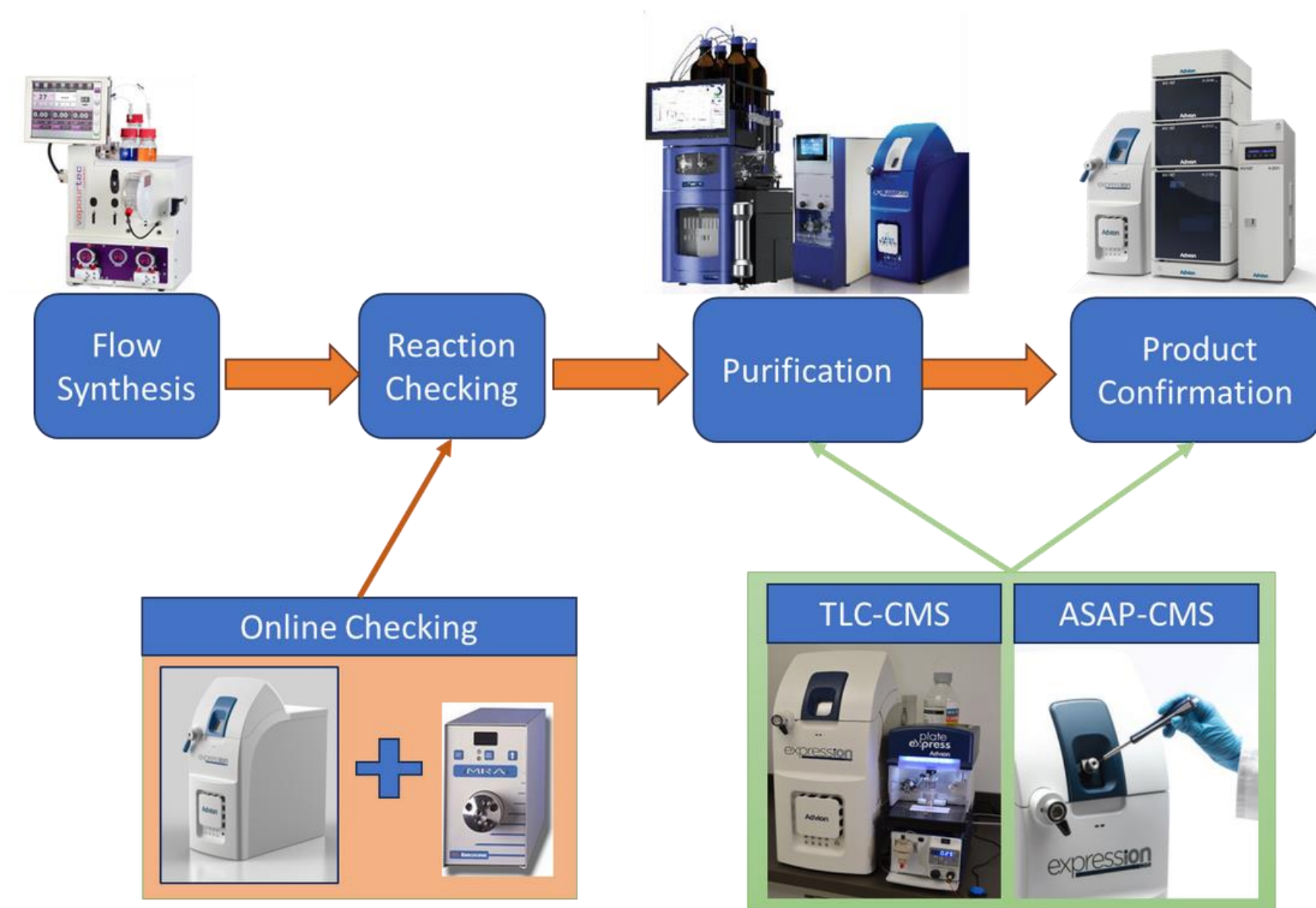
Expanding the Tool Kit of Automated Flow Synthesis: *General sequence for Organic synthesis work-flow*



Expanding the Tool Kit of Automated Flow Synthesis: *General sequence for Natural product and derivatization*



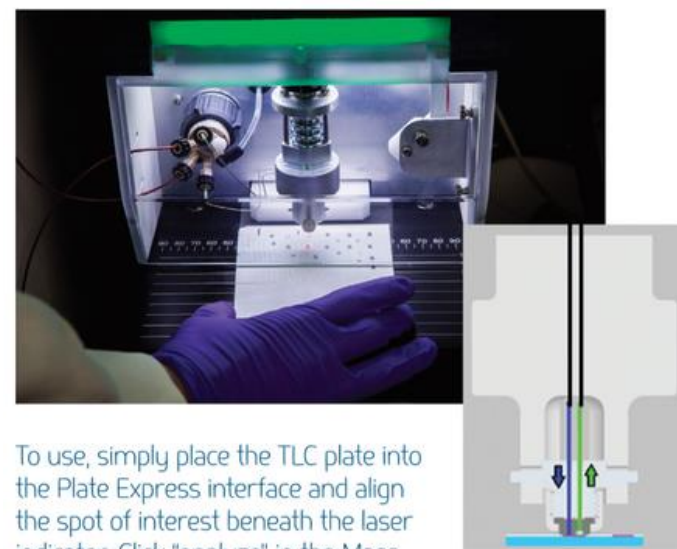
Expanding the Tool Kit of Automated Flow Synthesis: *Development of In-line Flash Chromatography Purification*



Compact Mass Spectrometer : Novel Central System for Organic Synthesis



Compact Mass Spectrometer : Novel Central System for Organic Synthesis

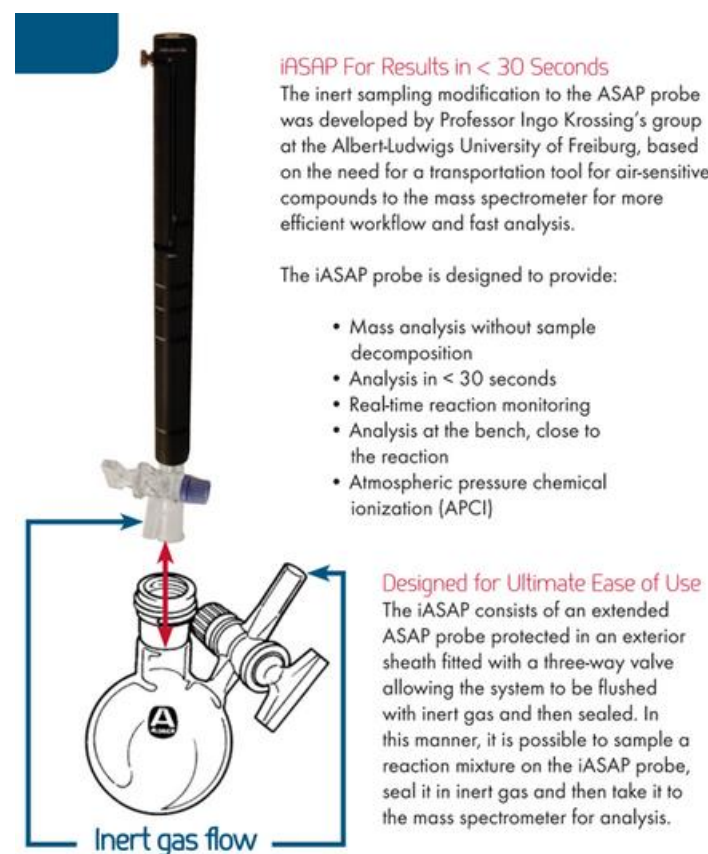
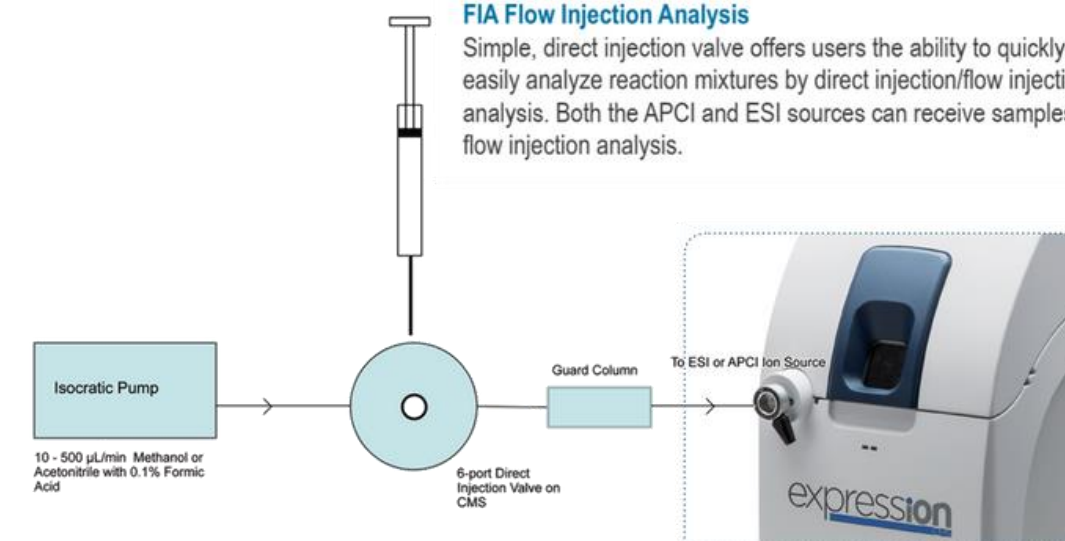


To use, simply place the TLC plate into the Plate Express interface and align the spot of interest beneath the laser indicator. Click "analyze" in the Mass Express software.



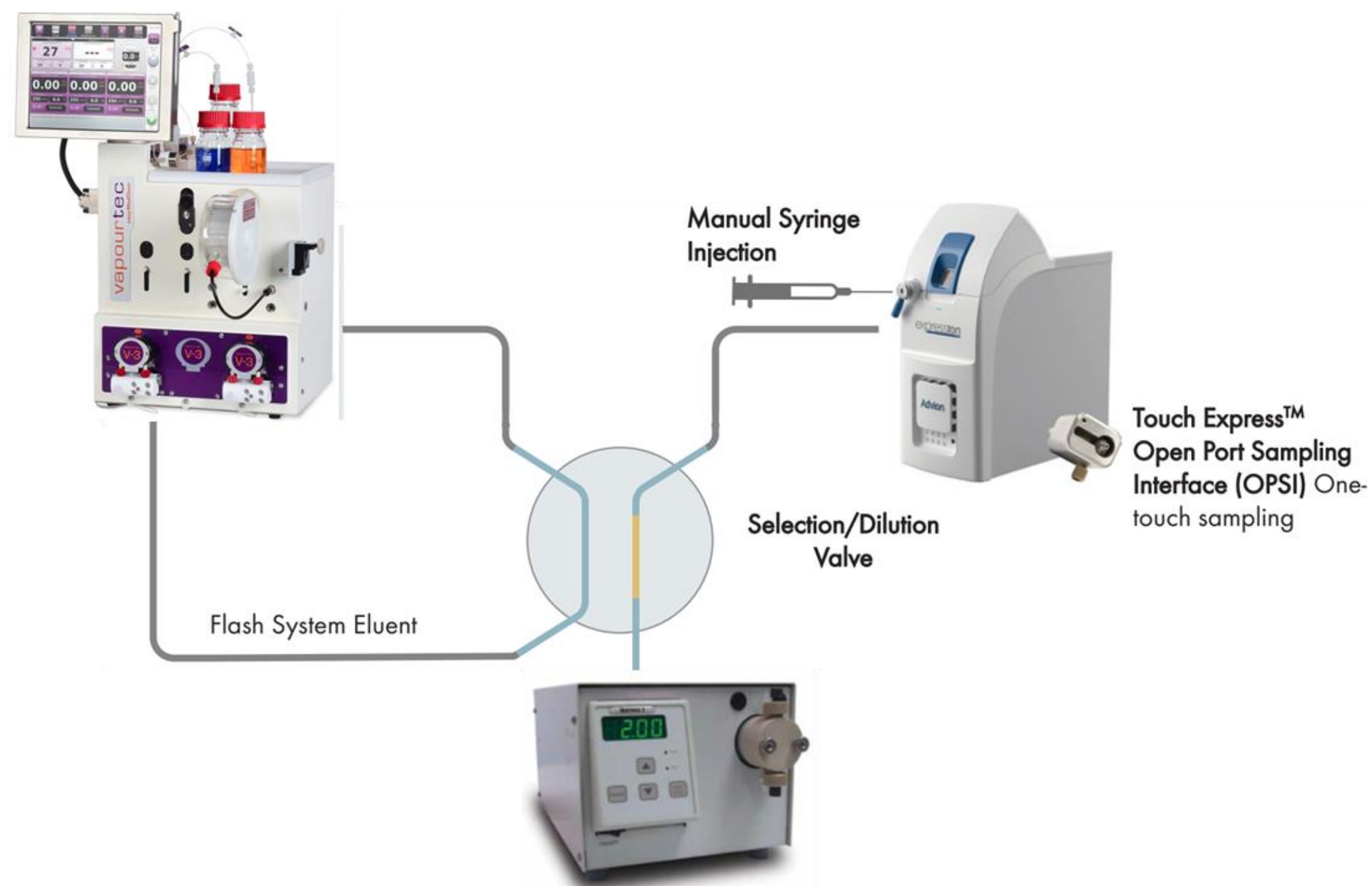
Direct Injection & FIA Flow Injection Analysis

Simple, direct injection valve offers users the ability to quickly and easily analyze reaction mixtures by direct injection/flow injection analysis. Both the APCI and ESI sources can receive samples for flow injection analysis.





Compact Mass Spectrometer : *Flow Chemistry Monitoring*



Compact Mass Spectrometer : *Flow Chemistry Monitoring*



Combined flash chromatography, TLC, (U)HPLC and manual injection interface. No re-plumbing necessary.



ASAP & iASAP probes for liquids, solids & air-sensitive samples



Manual Syringe Injection

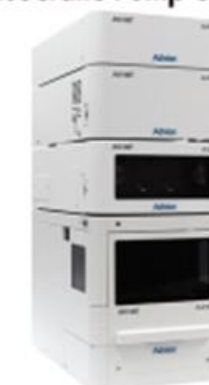


Touch Express™ Open Port Sampling Interface (OPSI) One-touch sampling

Flash System Eluent

Selection/Dilution Valve

Isocratic Pump or HPLC

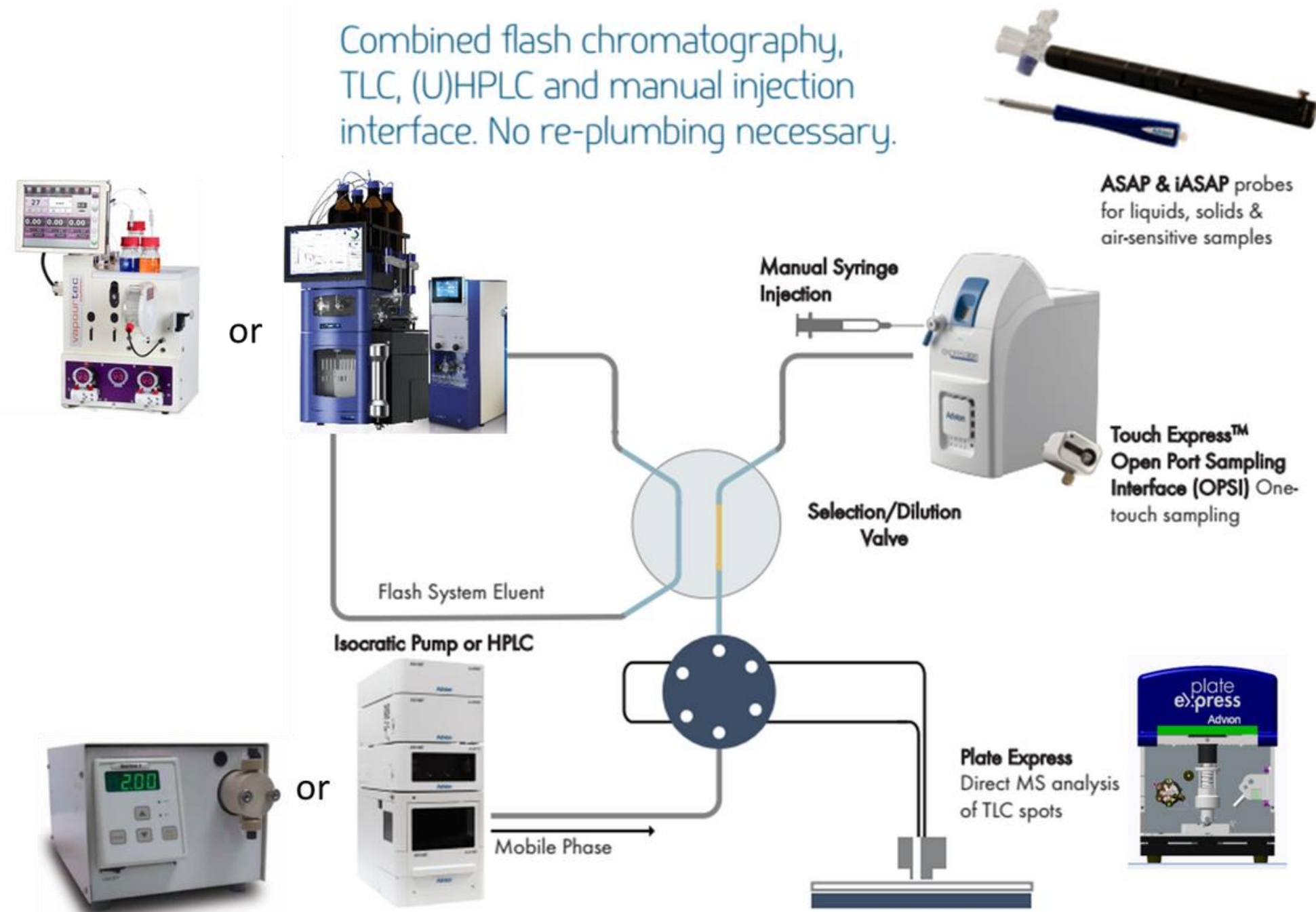


Mobile Phase

Plate Express
Direct MS analysis of TLC spots



Expanding the Tool Kit of Automated Flow Synthesis: *Development of In-line Flash Chromatography Purification*



A Complete Benchtop Solution

The **expression** CMS with the Plate Express TLC plate reader, customizable (U)HPLC, the ASAP and iASAP probes for liquids, solids and even inert compounds, the Touch Express Open Port Sampling Interface (OPSI) plus a direct injection interface - all at the bench.

These techniques include:

- Plate Express® TLC Plate Reader
- Atmospheric Solids Analysis Probe (ASAP®)
- InertAtmospheric Solids Analysis Probe (iASAP)
- Touch Express™ Open Port Sampling Interface (OPSI)
- Volatile APCI (vAPCI)
- AVANT™ Modular (U)HPLC
- Direct Injection/Flow Injection Analysis (FIA)

The CMS also directly interfaces with:

- Flow Chemistry
- Flash Chromatography
- Preparative Liquid Chromatography (Prep-LC)
- Supercritical Fluids Chromatography (SFC)

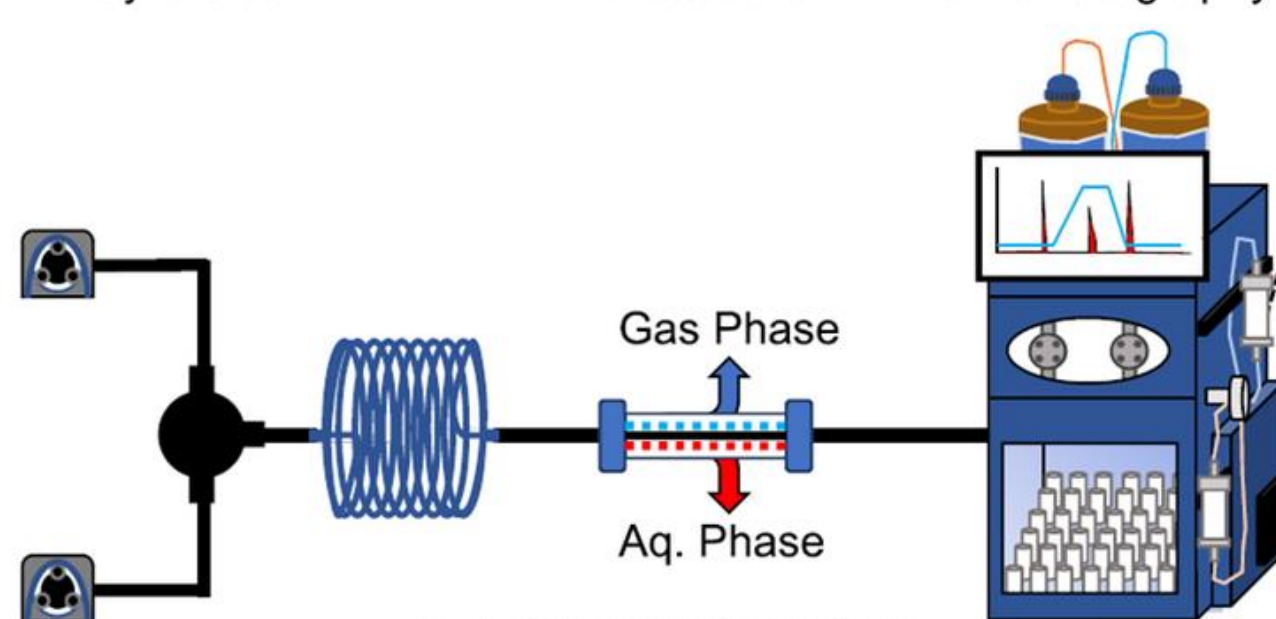
Expanding the Tool Kit of Automated Flow Synthesis: *Development of In-line Flash Chromatography Purification*

This Work: Continuous Flash Column Chromatography

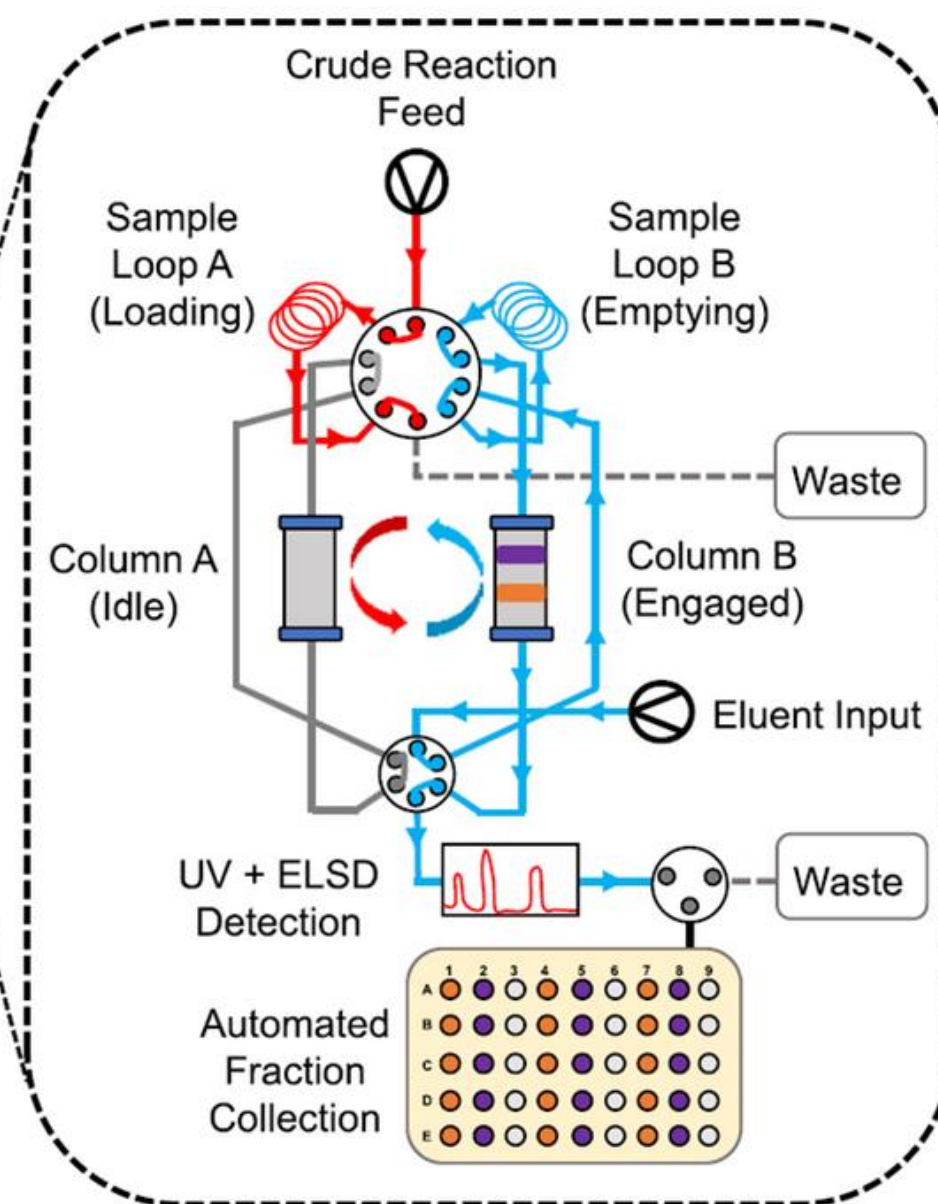
Continuous Flow Synthesis

In-Line Extractions

In-Line Flash Chromatography



- Four example systems.
- Up to >99% purity (LC-MS).
- Up to 9.9 mmol/h productivity with concurrent isolation of by-product at 7.7 mmol/h.

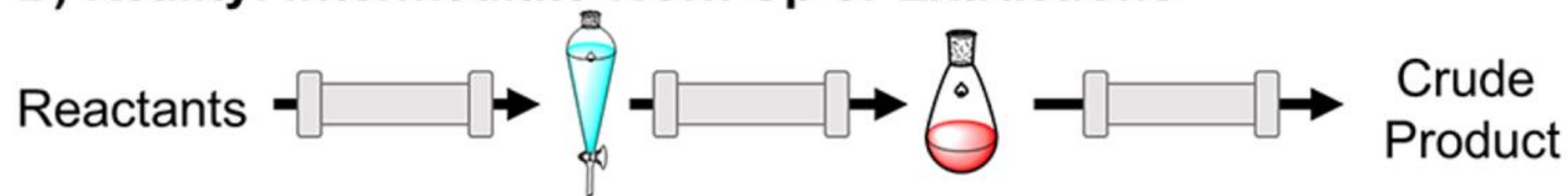


Expanding the Tool Kit of Automated Flow Synthesis: *Development of In-line Flash Chromatography Purification*

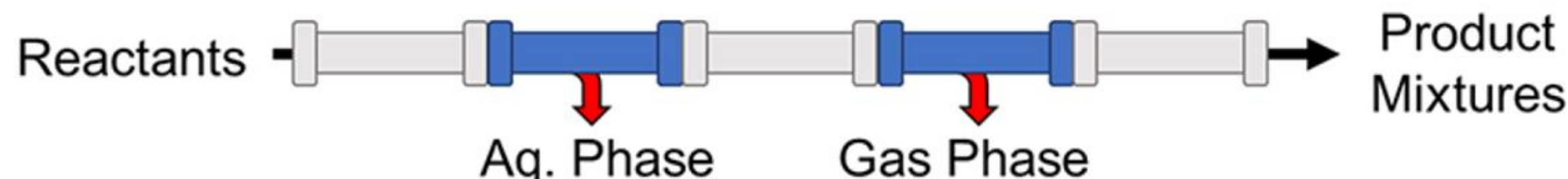
A) Ideal: Continuous Isolation of Pure Product



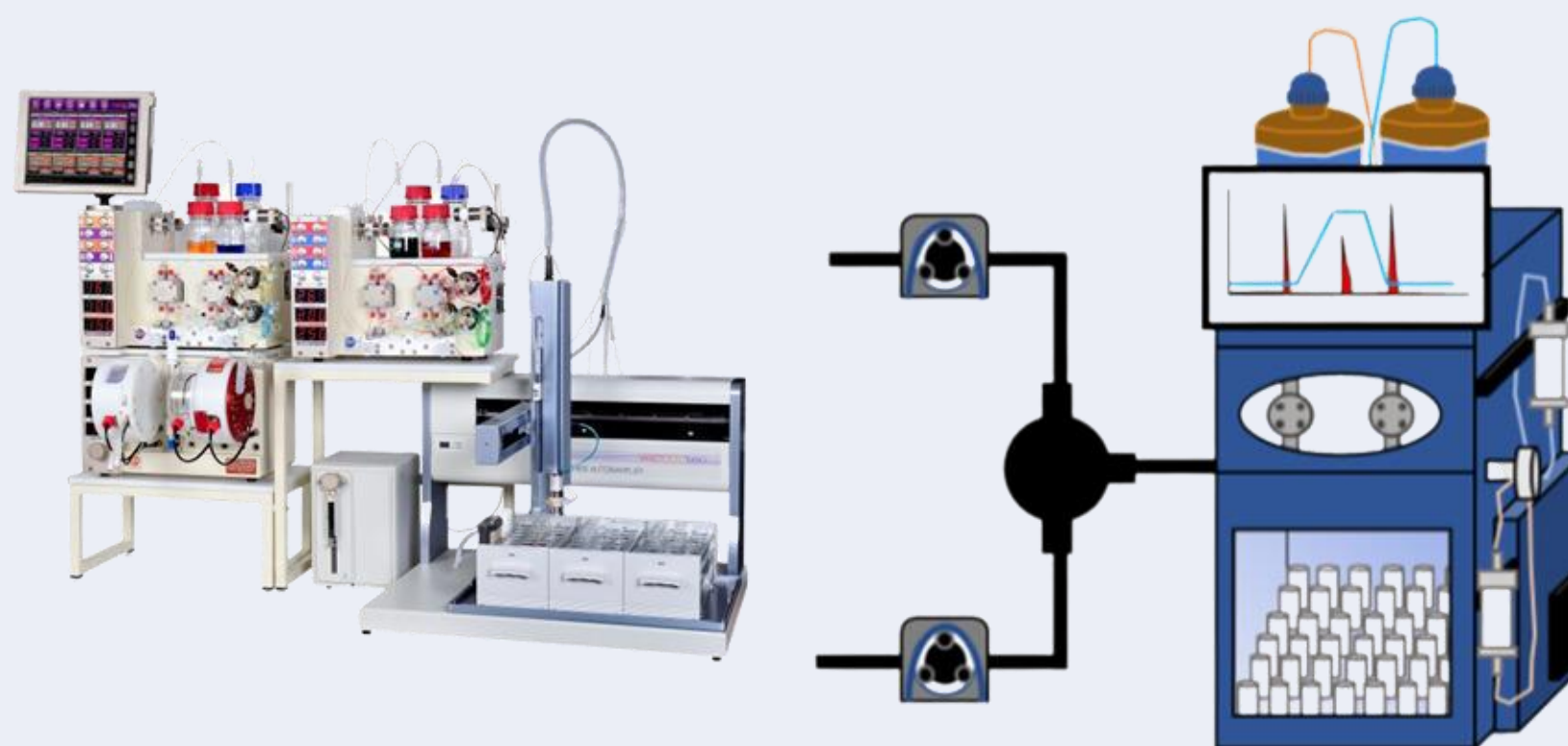
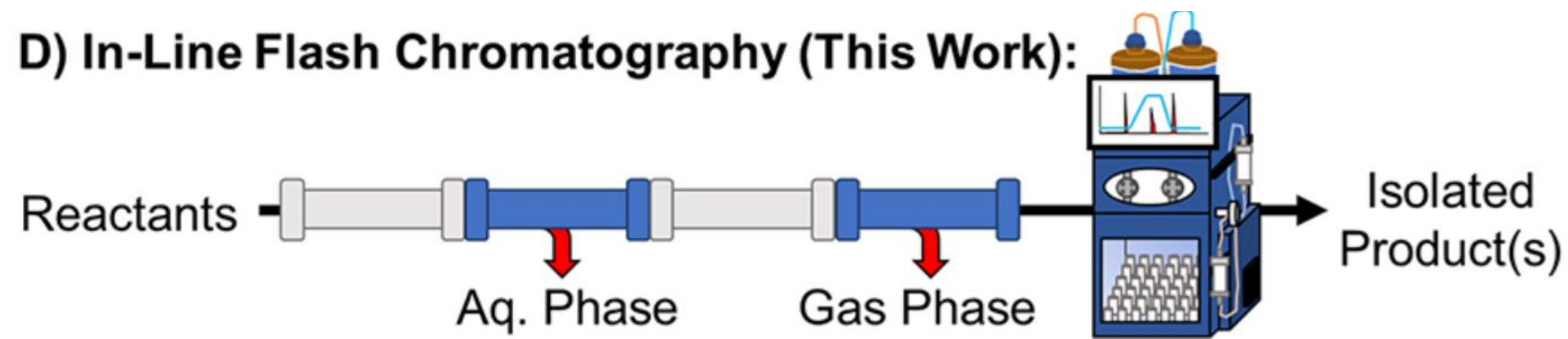
B) Reality: Intermediate Work-Up or Extractions



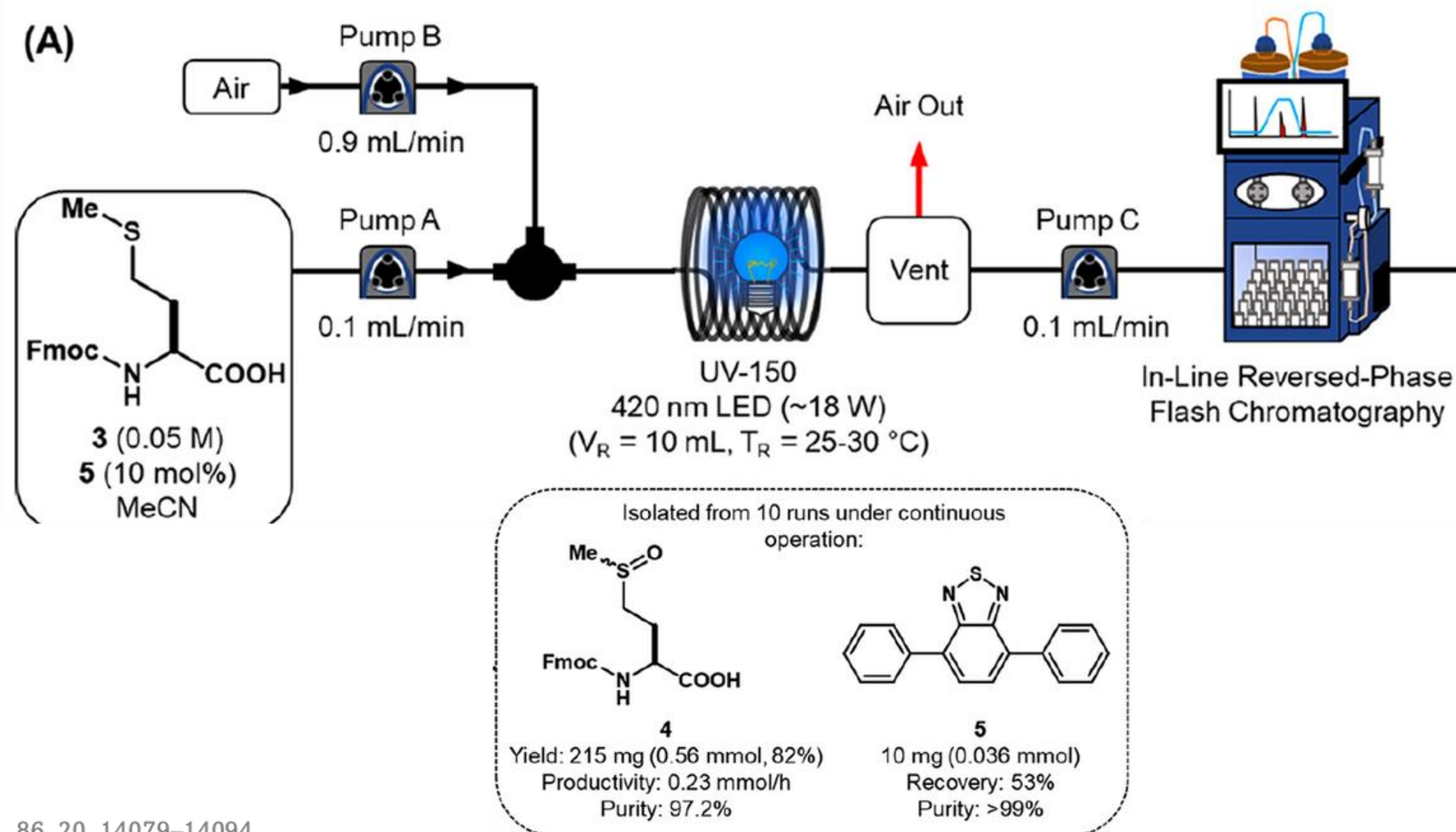
C) In-Line Extractions: Continuous Production of Product Mixtures



Expanding the Tool Kit of Automated Flow Synthesis: *Development of In-line Flash Chromatography Purification*



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Any Questions?

