

CO-DRIVEN SULFOXIMINOCARBONYLATION OF ARYL HALIDES IN CONTINUOUS FLOW

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Sustainable Organic Synthesis & Catalysis

ABSTRACT

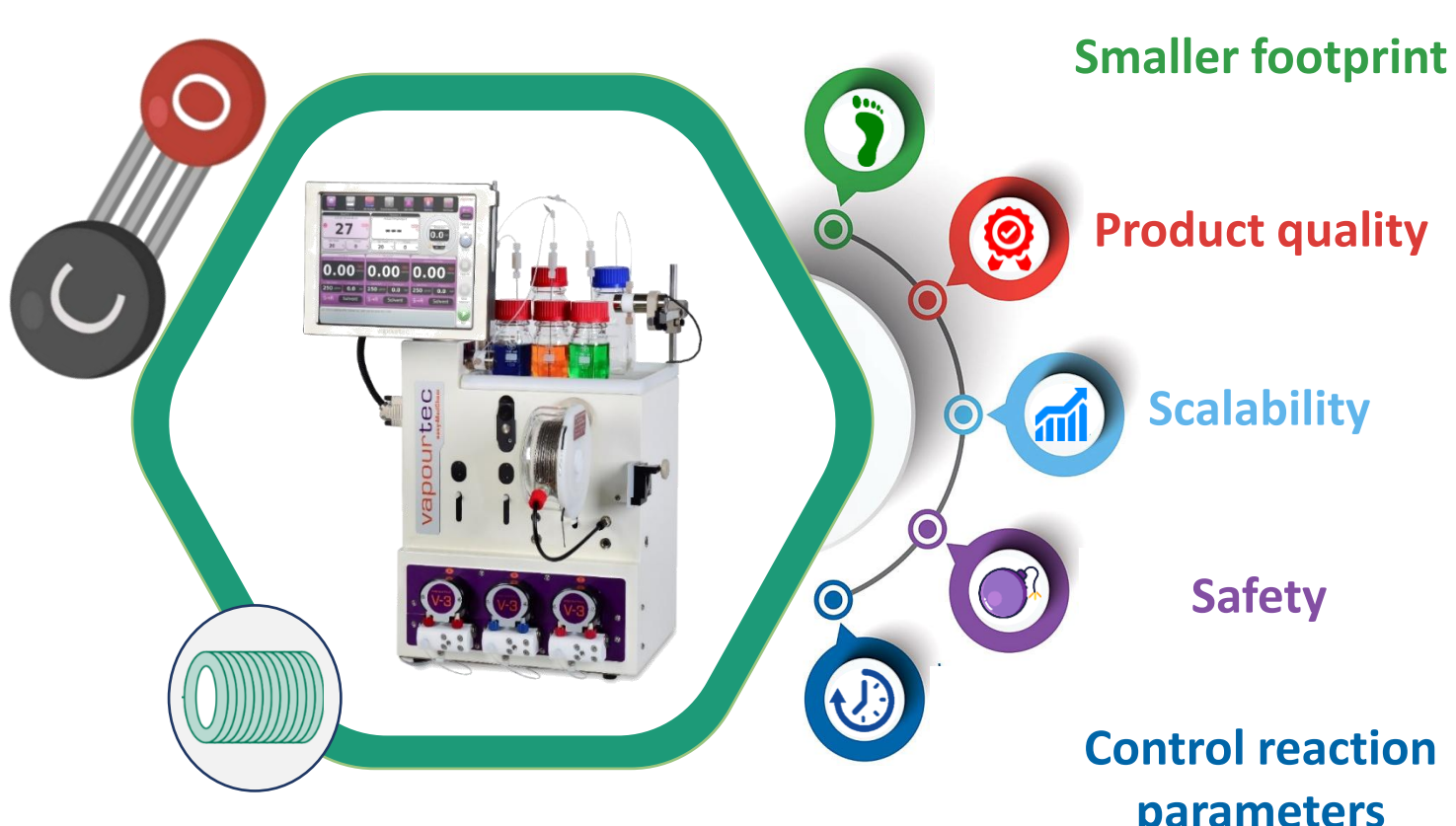
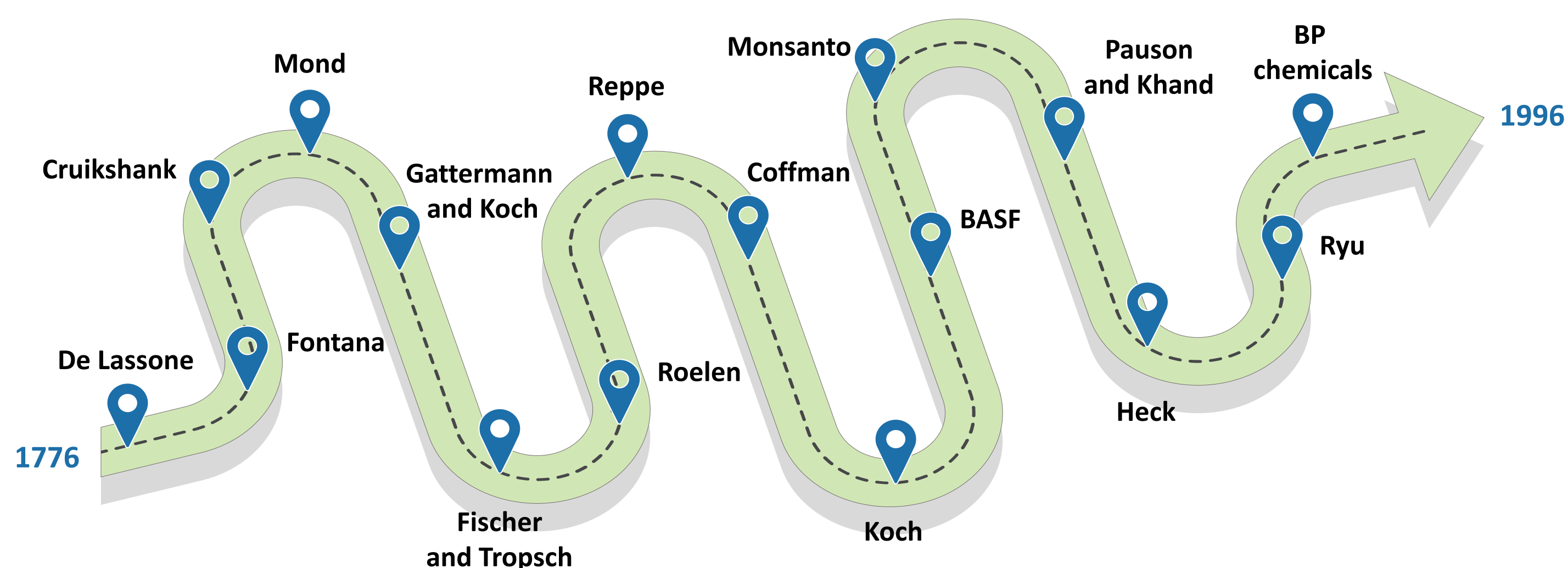
Carbonylation reactions play a crucial role in organic and industrial chemistry, enabling the introduction of carbonyl groups into organic substrates using carbon monoxide (CO). While CO is a cost-effective and atom-efficient reagent, its toxicity and low solubility present significant challenges in traditional batch processes. In recent years, flow chemistry has revolutionized these transformations, offering enhanced efficiency, safety, and precise control of reaction parameters.

Sulfoximines are valuable scaffold in pharmaceutical, agricultural, and organic chemistry as chiral auxiliaries and intermediates. Despite their synthetic potential, previous approaches often rely on toxic reagents, excessive oxidants, and tedious purification steps, leading to low conversions and undesirable by-products.

Here, we report a continuous flow protocol for the *N*-arylation of different functionalized aryl halides with sulfoximines under CO pressure using a palladium-based catalyst, a base, and a ligand. Comprehensive screening of organic bases in batch mode allowed to identify optimal conditions, which were then translated into a flow system operating at 80 °C and 6 bar for 40 minutes. This innovative strategy provides rapid reactions, high selectivity, and excellent yields (from 79 to > 99%) across a small library, demonstrating the advantages of continuous flow technology in carbonylation chemistry.

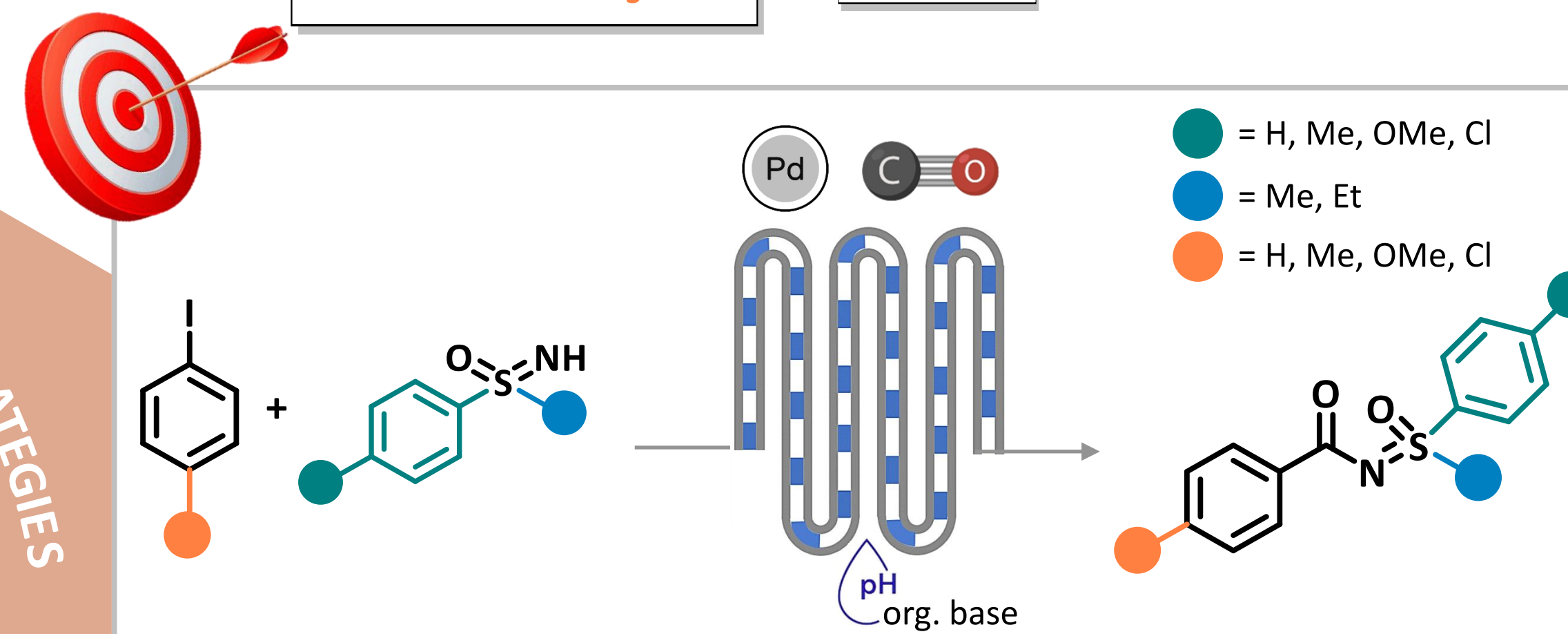
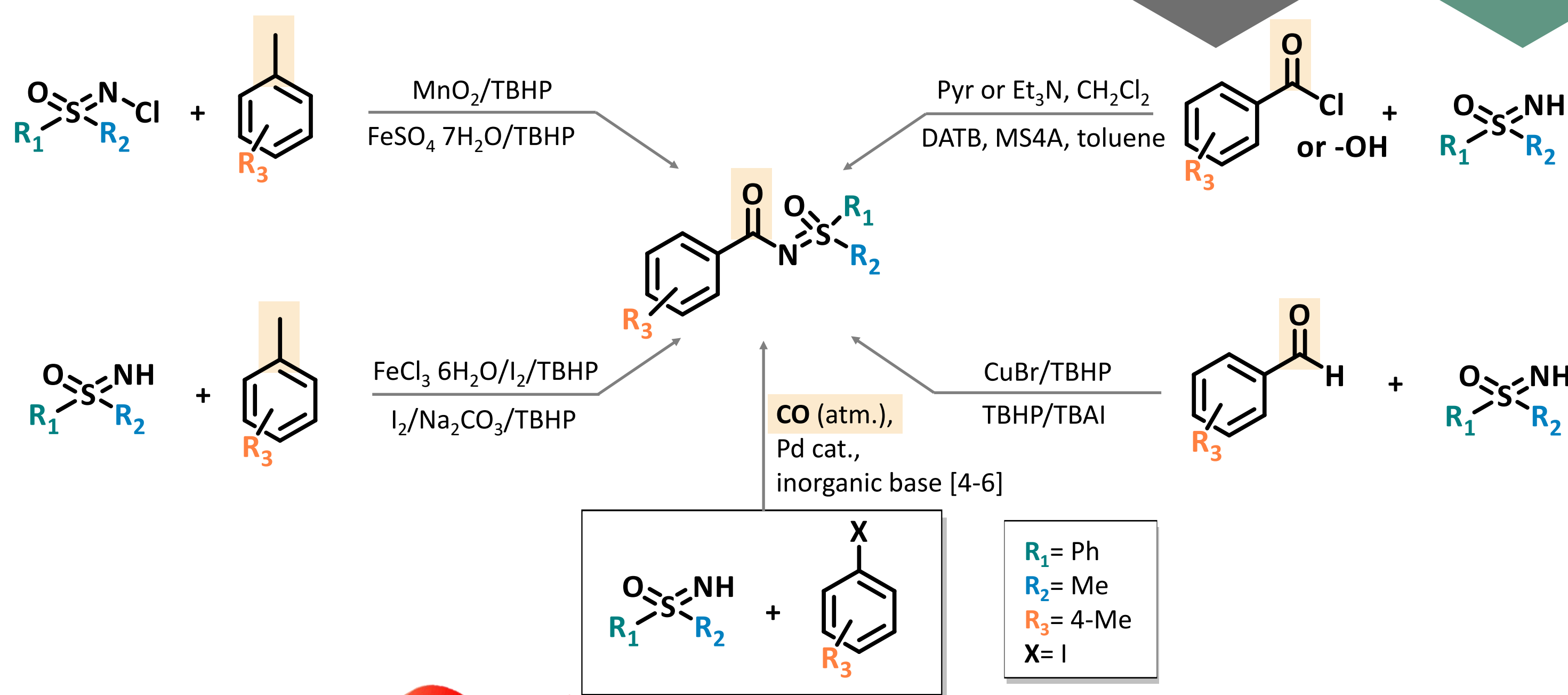
CARBONYLATION REACTIONS AND FLOW CHEMISTRY

Carbonylation reactions involve the incorporation of CO into organic molecules. Initially feared for its toxicity, CO is now essential in various applications, with carbonylation chemistry achieving major advancements in both industry and academic research. [1]

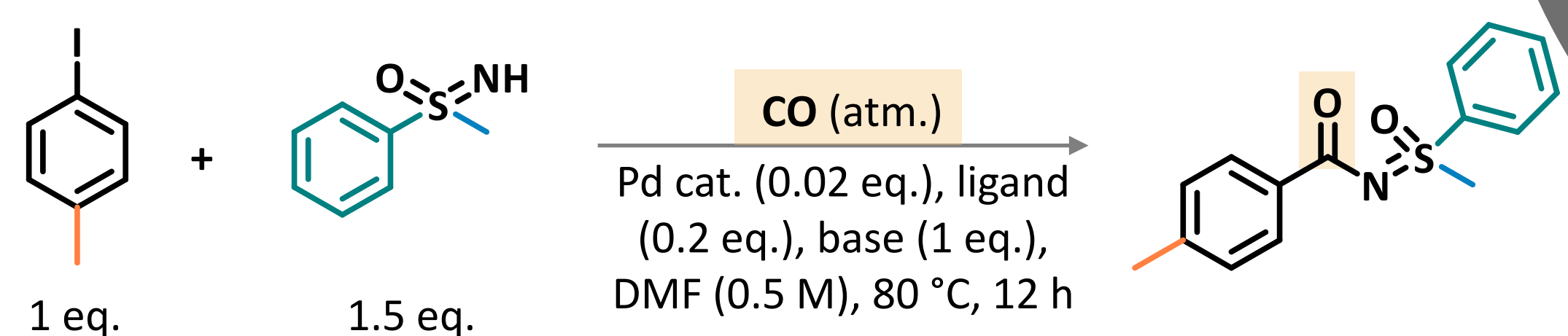


Flow technology is ideal for gas-liquid transformations, especially those involving toxic gases (i.e., CO). It ensures precise dosing, high T and P conditions, and safe handling of hazardous reagents. [2, 3]

BACKGROUND RESEARCH [4]



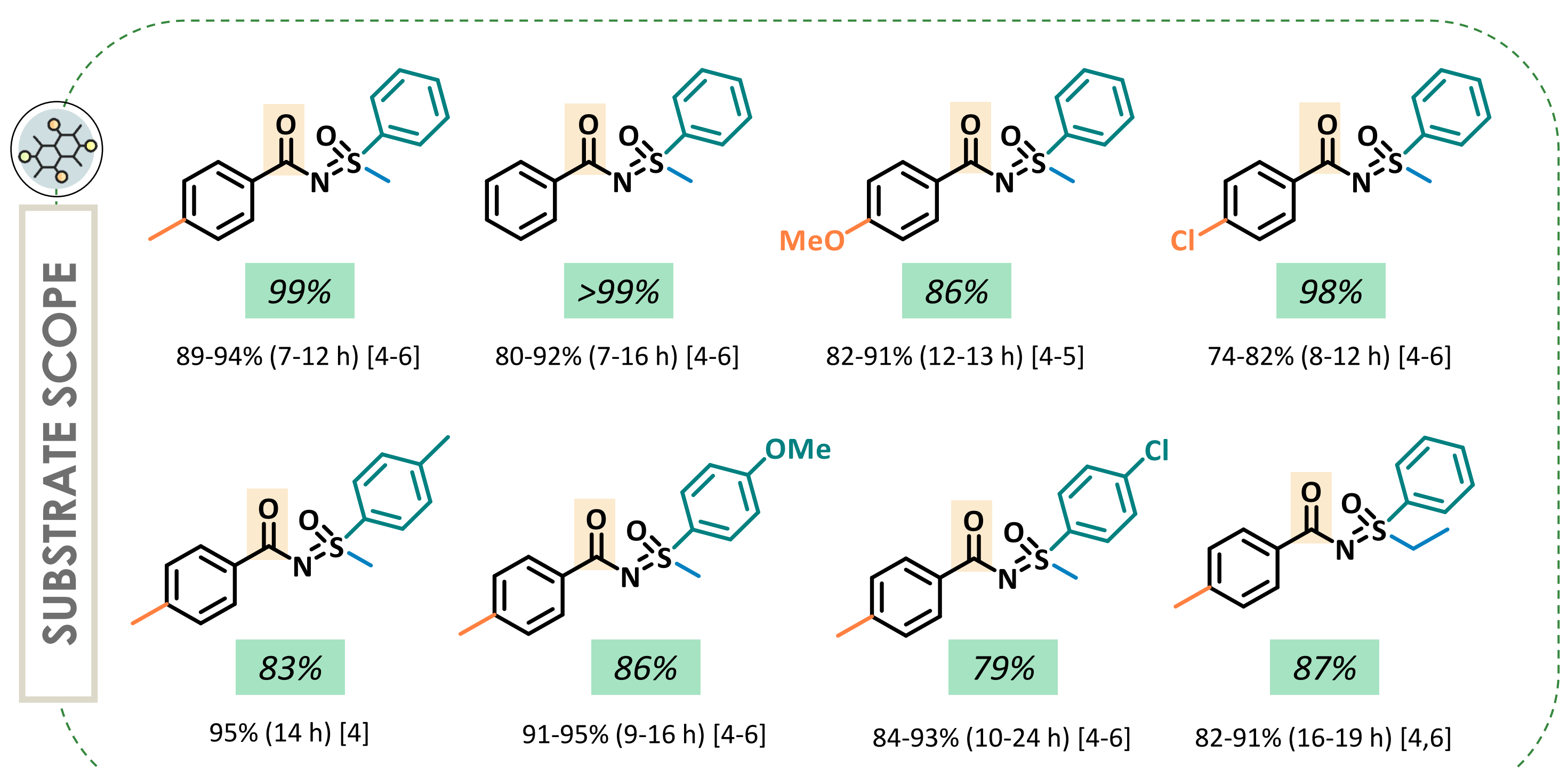
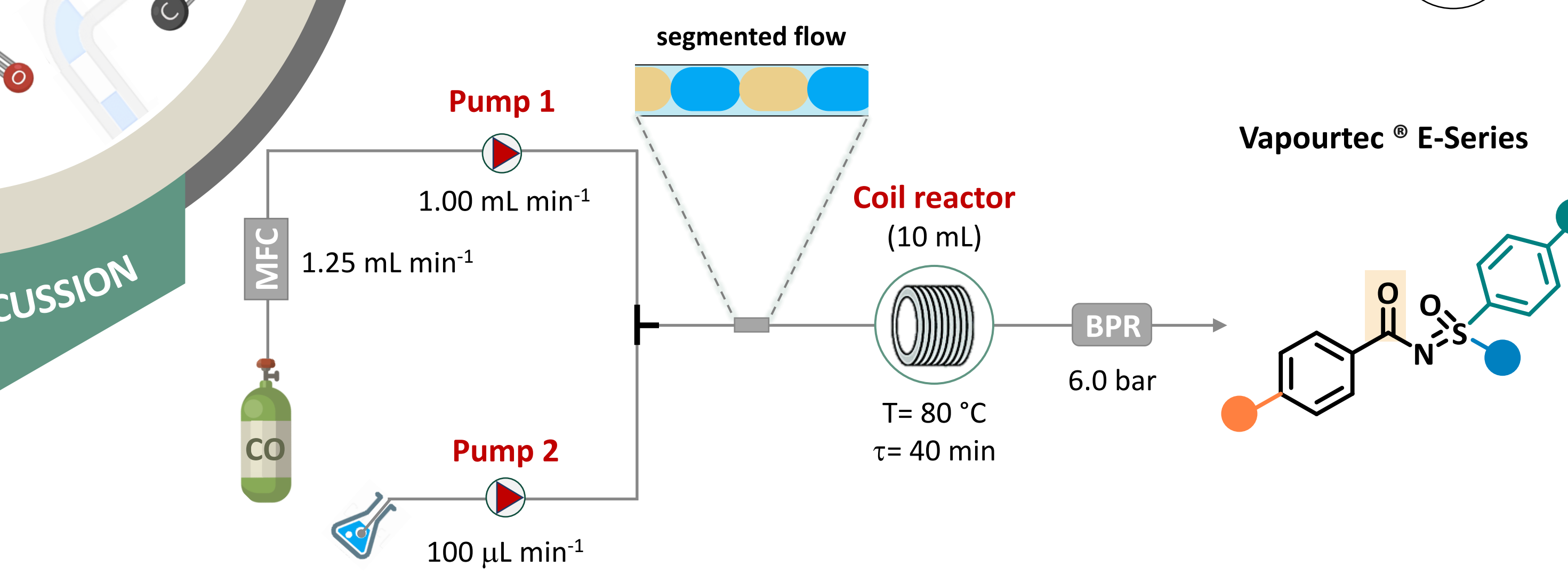
SCREENING IN BATCH MODE



Entry	Catalyst	Ligand	Base	Conversion (%) ^a
1 [6]	Pd/C	-	K ₂ CO ₃	70
2	Pd(OAc) ₂	-	K ₂ CO ₃	91
3	Pd(OAc) ₂	N-xantphos	K ₂ CO ₃	>99
4	Pd(OAc) ₂	N-xantphos	DIPEA	>99
5	Pd(OAc) ₂	N-xantphos	pyridine	46
6	Pd(OAc) ₂	N-xantphos	DBU	>99
7	Pd(OAc) ₂	N-xantphos	Et ₃ N	>99
8	Pd(OAc) ₂	N-xantphos	TBAF	>99
9	Pd(OAc) ₂	N-xantphos	pyrrolidine	>99
10	Pd(OAc) ₂	N-xantphos	DMAP	>99
11	Pd(OAc) ₂	N-xantphos	morpholine	>99
12	Pd(OAc) ₂	N-xantphos	piperidine	78
13	Pd(OAc) ₂	N-xantphos	DABCO	>99

All reactions were performed with 0.5 mmol iodotoluene in 1 mL of DMF for 12 hours at 80 °C. ^a Determined by ¹H-NMR of the crude reaction mixture by comparing the methyl of tolyl group (3H, s) of the reaction product (2.40 ppm) with the methyl group of iodotoluene (2.29 ppm) of the reaction mixture or aromatic protons in α -positions of tolyl groups (2H, m) (7.23-7.18 reaction product and 6.94-6.90 ppm iodotoluene).

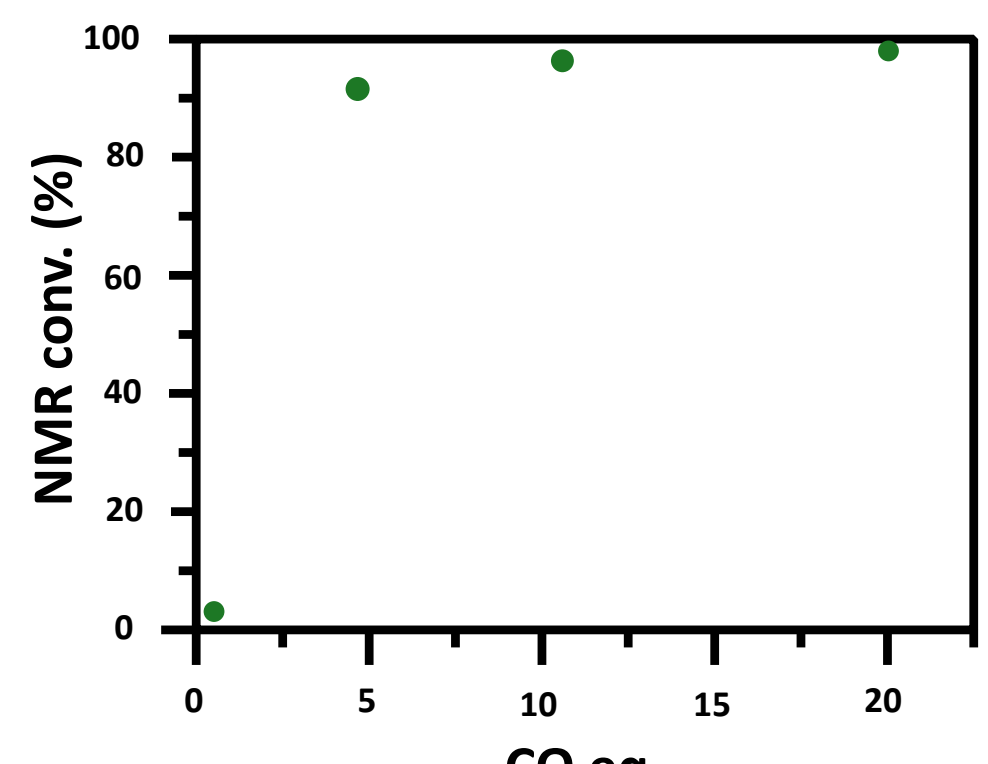
OPTIMIZATION OF FLOW PARAMETERS



RESULTS AND DISCUSSION

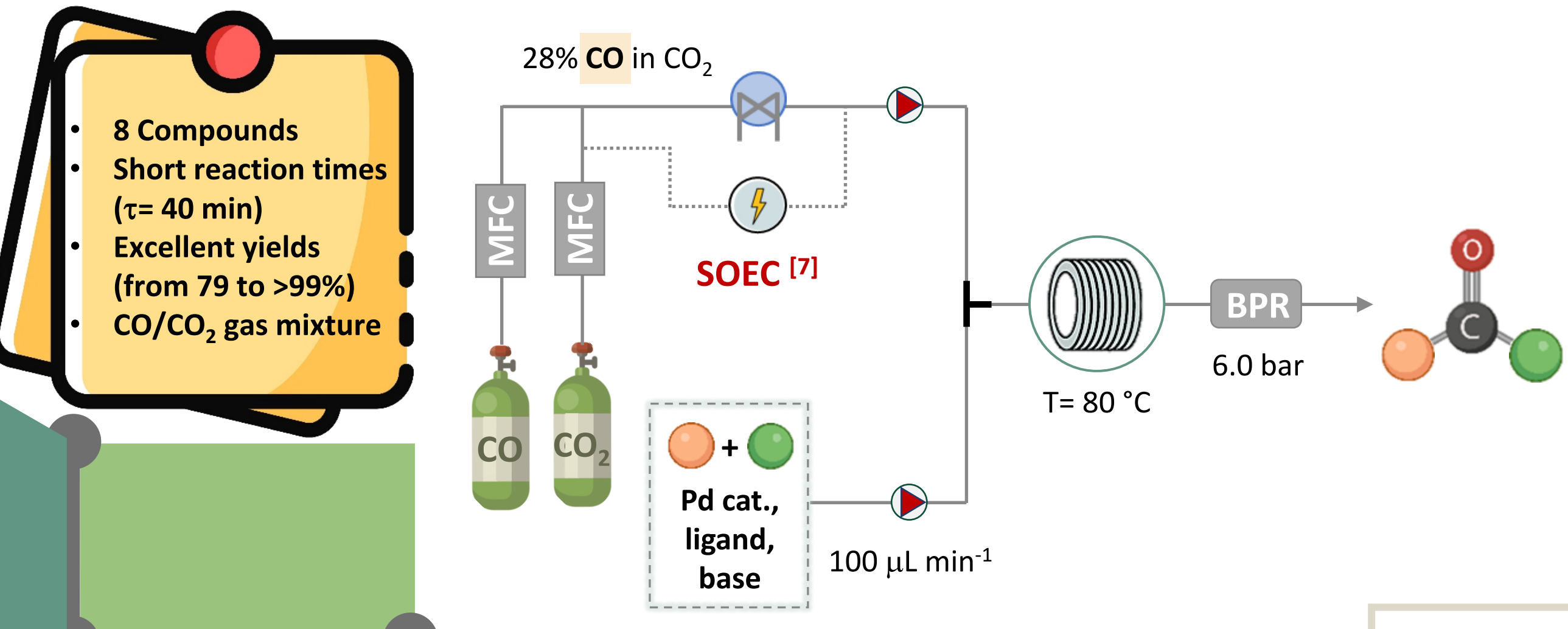
Entry	Pump 1 flow rate (mL min ⁻¹)	MCF CO flow rate (mL min ⁻¹)	MCF tot flow rate (mL min ⁻¹)	Residence time (t, min)	CO eq. ^a	Conversion (%) ^b
1	3.60	1.25	4.45	40	20	>99
2	1.80	0.62	2.22	20	5	90-92
3	2.40	0.93	3.33	30	11	99

All reactions were performed with 0.5 mmol iodotoluene in 1 mL of DMF. The reaction mixture was pumped, mixed with a stream of CO in CO₂ at variable flow rates (28% of CO in CO₂), and reacted inside a 10 mL coil-reactor at 80 °C and 6 bar (BPR). ^a Determined according to the equation $nCO = P(atm) V(L) / RT(K)$. ^b Determined by ¹H-NMR of the crude reaction mixture.



$$nCO = \frac{P(atm) V(L)}{RT(K)}$$

CO/CO₂ GAS MIXTURE



- 8 Compounds
- Short reaction times ($\tau = 40$ min)
- Excellent yields (from 79 to >99%)
- CO/CO₂ gas mixture

