



UNIVERSITÀ DEGLI STUDI DI MILANO

# Stereoselective Synthesis Mediated by Light and Electricity

*Speaker Dr. Fabrizio Medici*

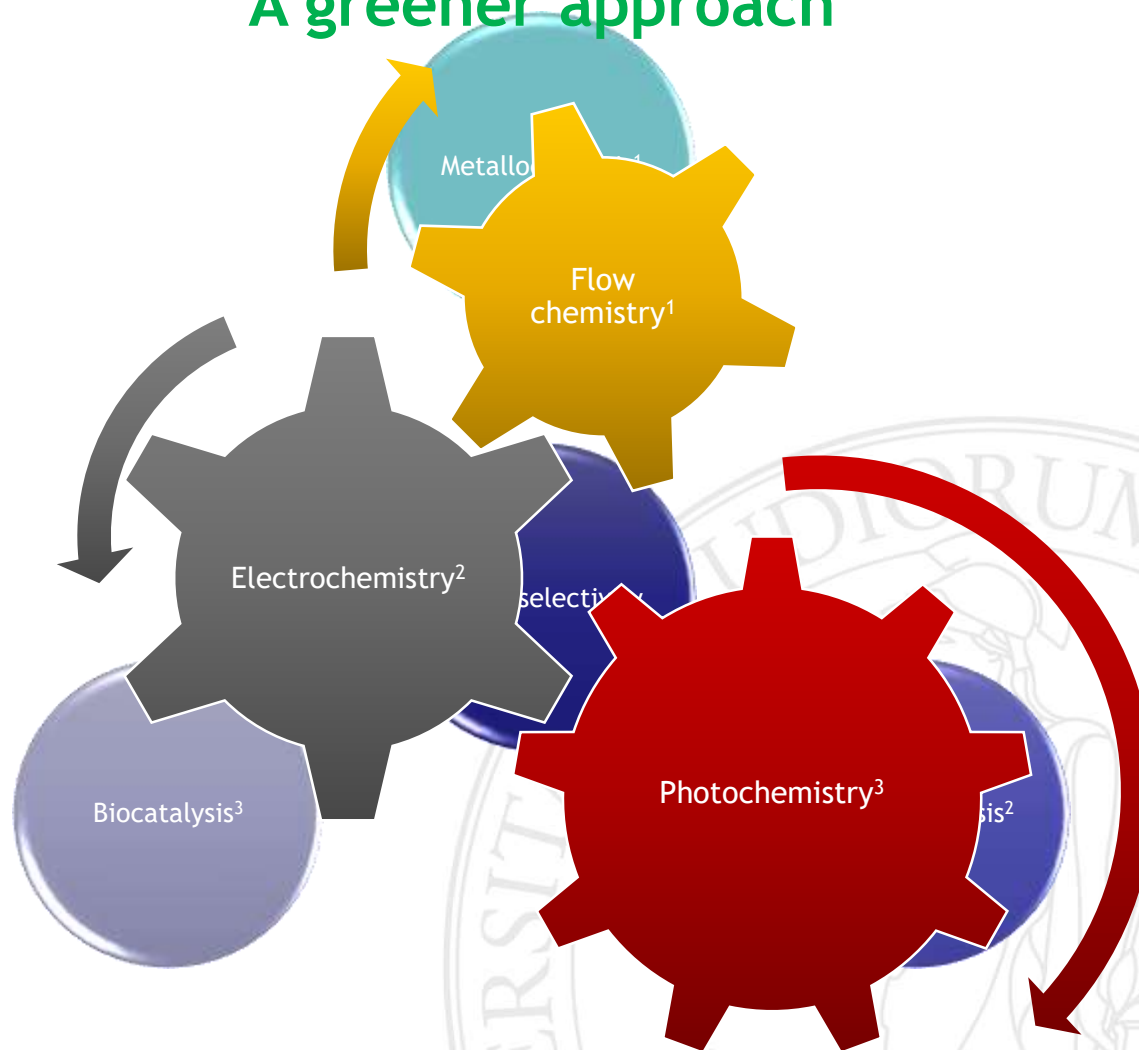
*Tenure Track Assistant Professor on NextGeneration-EU  
Project MUSA:*

*Multilayered Urban Sustainability Action; Università degli  
Studi di Milano*

*fabrizio.medici@unimi.it*

# Stereoselection: Key Role in Chemistry

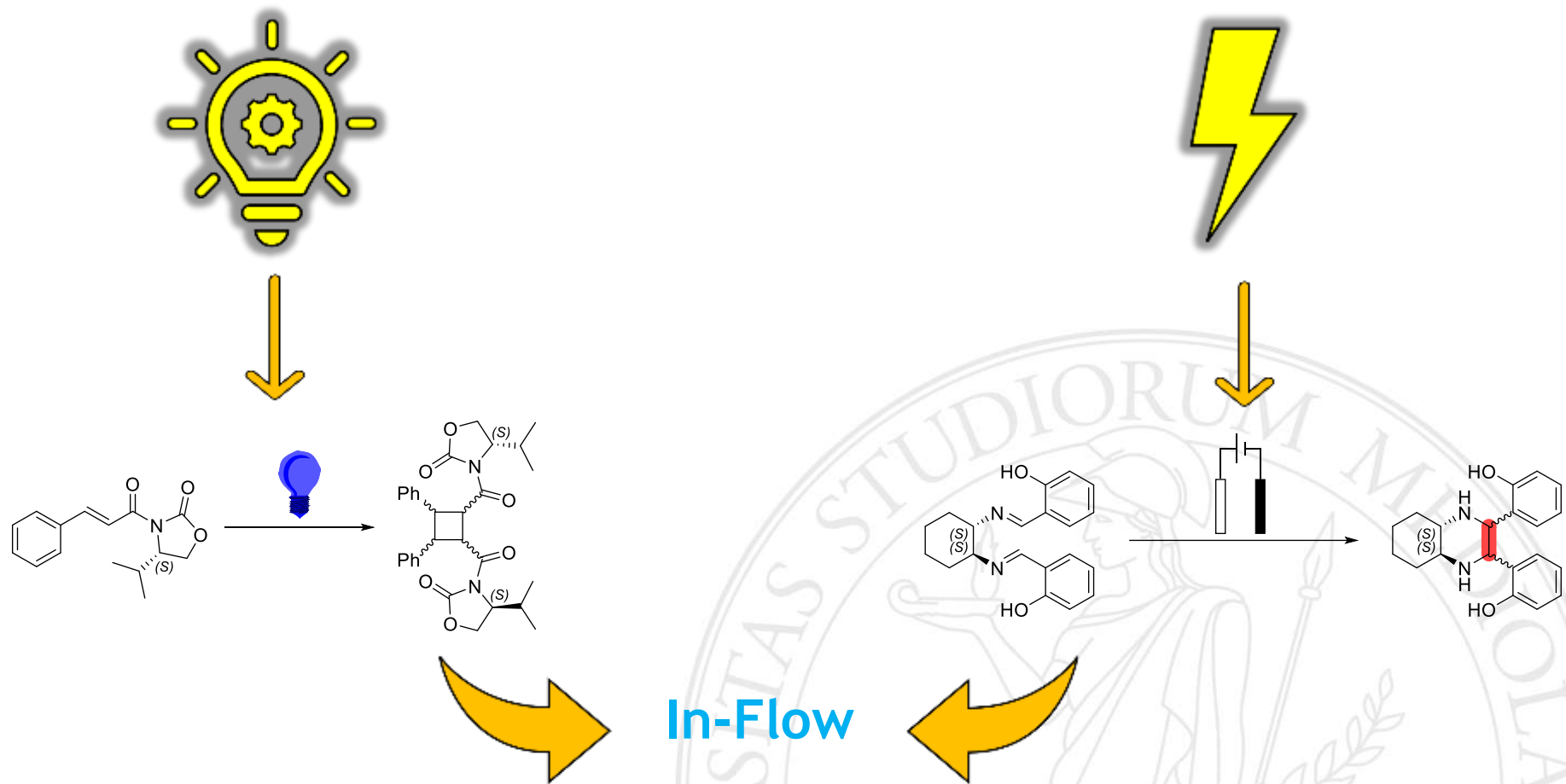
A greener approach



1. [Kleschik, M.; Sheng, L.; Wang, G.; Wang, S. Stereoselective Asymmetric Vacant Transition Metal Catalysis. \*Chem Rev\* 2023, 23 \(6\), 4764-4794.](#) Sustainability of Flow Chemistry and Microreaction Technology.
  2. [García-Camacho, J. D.; García-Rodríguez, J. M. Developments and Trends in Asymmetric Organocatalysis. \*European Journal of Organic Chemistry\* 2023, 26 \(1\), e202200950.](#)
  3. [Kumar, M.; Al-Jarrah, A. J. Green Chemistry: A Way to Green and Sustainable Biocatalysis. \*Methods in Enzymology\* 2020, 619, 19-30.](#) Synthesis of Pharmaceutical Building Blocks\*. *Biocatalysis and Biomimetic Chemistry* 2018, 16 (2), 112-130.
3. [Meingast, M. The 2018 Nobel Prize in Chemistry: Clean up by Going Green. \*Nat Rev Chem\* 2017, 1 \(11\), 1-1.](#)



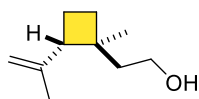
# Our Projects



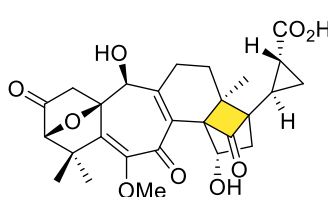


# Stereoselective [2+2] photocycloaddition: a Viable Strategy for the Synthesis of Enantiopure Cyclobutane Derivatives.

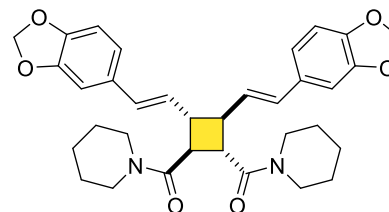
## Cyclobutanes in drugs



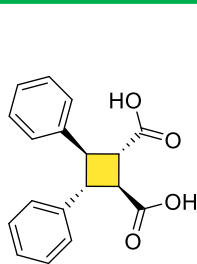
(±)-Fragranol



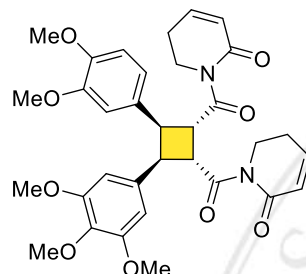
Solanoeclepin A



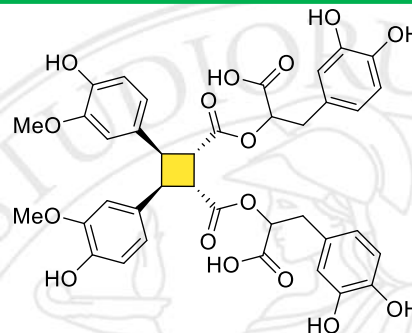
(±)-Nigramide



Truxinic acid



Piperarborenine D



Sagerinic acid

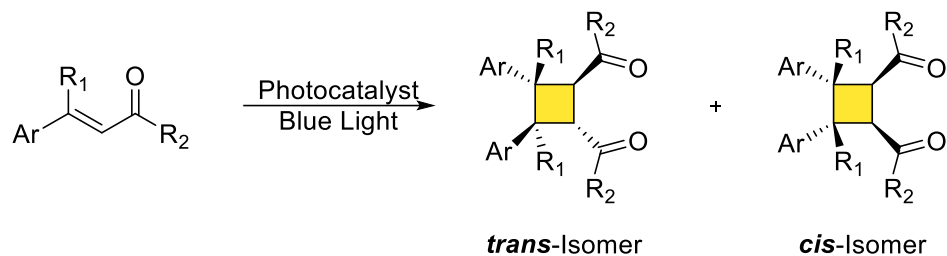
[2+2] cycloaddition from  
cinnamic derivatives

1. van der Kolk, M. R.; Janssen, M. A. C. H.; Rutjes, F. P. J. T.; Blanco-Ania, D. Cyclobutanes in Small-Molecule Drug Candidates. *ChemMedChem* **2022**, *17* (9), e202200020.
2. Ren, S.; Pan, F.; Zhang, W.; Rao, G.-W. Molecules Containing Cyclobutyl Fragments as Therapeutic Tools: A Review on Cyclobutyl Drugs. *Current Medicinal Chemistry* **2022**, *29* (23), 4113-4135.
3. Bauer, M. R.; Fruscia, P. D.; Lucas, S. C. C.; Michaelides, I. N.; Nelson, J. E.; Storer, R. I.; Whitehurst, B. C. Put a Ring on It: Application of Small Aliphatic Rings in Medicinal Chemistry. *RSC Med. Chem.* **2021**, *12* (4), 448-471.



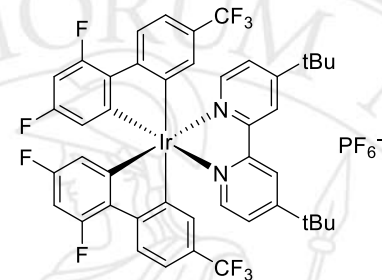
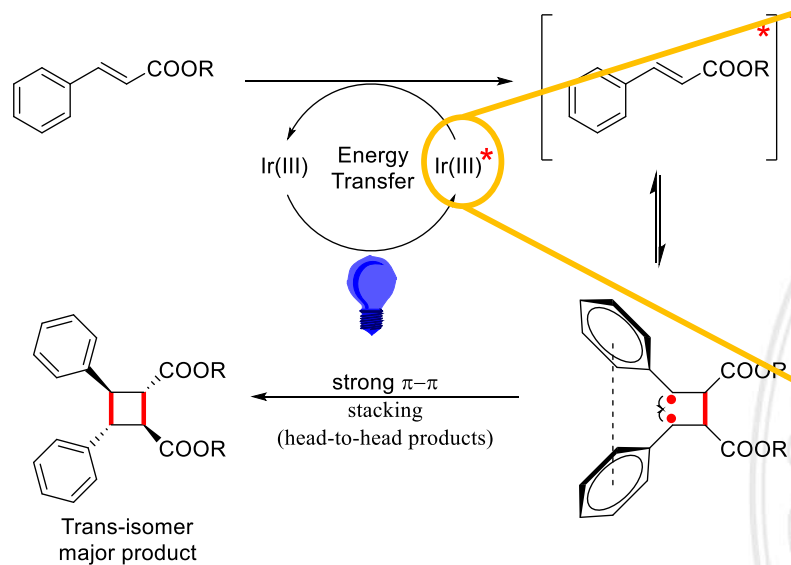


# Background



Yoon, T. P. *ACS Catal.* **2013**, *3* (5), 895–902.

## From Cinnamic Esters



$\text{Ir(III)}^*/\text{Ir(II)} = 1,21\text{V}$   
 $\text{Ir(III)}^*/\text{Ir(IV)} = -0,89\text{V}$   
 $\text{Ir(III)}/\text{Ir(II)} = -1,37\text{V}$   
 $\text{Ir(IV)}/\text{Ir(III)} = 1,69\text{V}$   
 $\text{Ir(III)}^* = 2300 \text{ ns}$

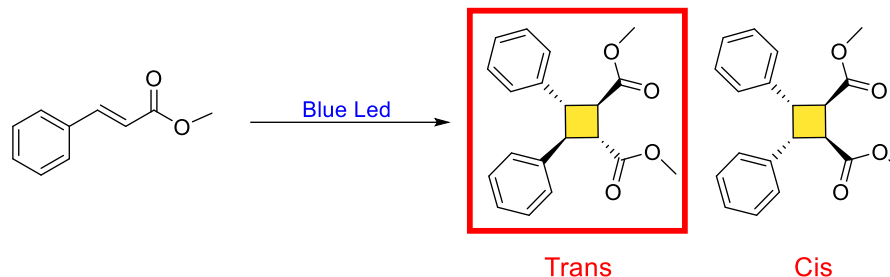
*Chem. Mater.* **2005**, *17* (23), 5712-5719.

Pagire, S. K.; Hossain, A.; Traub, L.; Kerres, S.; Reiser, O. *Chem. Commun.* **2017**, *53* (89), 12072-12075.





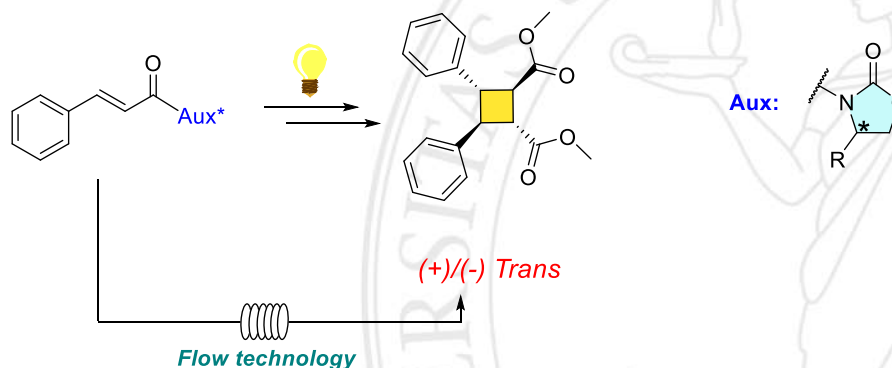
# Project Objective



Chen, L.-Y.; Huang, P.-Q. Evans' Chiral Auxiliary-Based Asymmetric Synthetic Methodology and Its Modern Extensions. *European Journal of Organic Chemistry* **2024**, 27 (4), e202301131.

## Control of the ABSOLUTE stereochemistry of the product

*Introduction of a chiral auxiliary in the molecule*

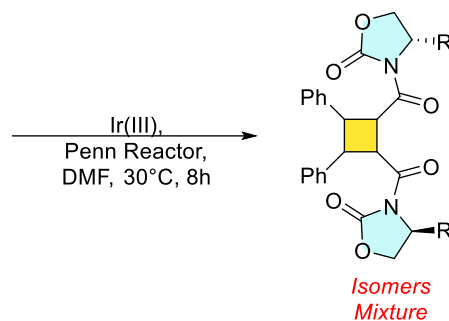
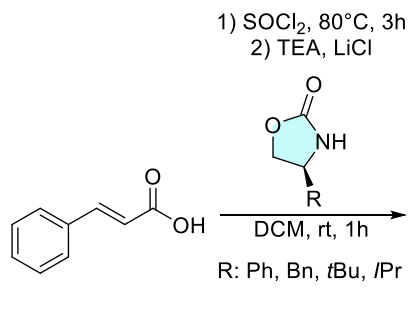


1. For the use of chiral auxiliaries in organocatalysed photoreaction: Medici, F.; Resta, S.; Presenti, P.; Caruso, L.; Puglisi, A.; Raimondi, L.; Rossi, S.; Benaglia, M., *Eur. J. Org. Chem.* **2021**, (32), 4521–4524.
2. For a review on chiral auxiliaries: a) Chen, L.-Y.; Huang, P.-Q. Evans' Chiral Auxiliary-Based Asymmetric Synthetic Methodology and Its Modern Extensions. *European Journal of Organic Chemistry* **2024**, 27 (4), e202301131. b) Diaz-Muñoz, G.; Miranda, I. L.; Sartori, S. K.; Rezende, D. C. de; Diaz, M. A. N., *Chirality* **2019**, 31 (10), 776-812.





# Synthetic Strategy

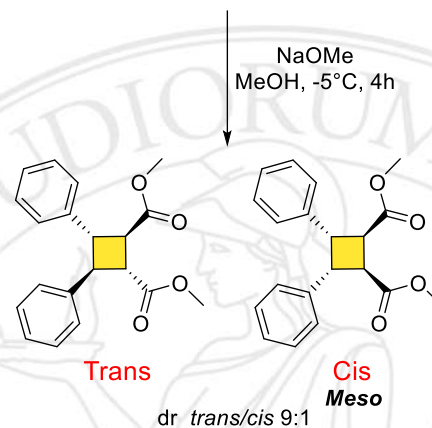


R:

- (*S*)-*t*Bu: 71% yield
- (*S*)-Bn: 58% yield
- (*S*)-Ph: 73% yield
- (*S*)-*i*Pr: 68% yield

R:

- (*S*)-*t*Bu: 79% ee
- (*S*)-Bn: 67% ee
- (*S*)-Ph: 71% ee
- (*S*)-*i*Pr: 93% ee;



**Absolute configuration trans-isomer:**  
1*R*, 2*R*, 3*S*, 4*S*  
 $\alpha_D^{20}$  [0,007 M in acetone]: -8,26

Green, B. S.; Hagler, A. T.; Rabinsohn, Y.; Rejtő, M. *Israel Journal of Chemistry* 1976, 15 (1-2), 124-130.

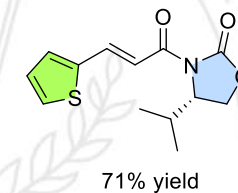
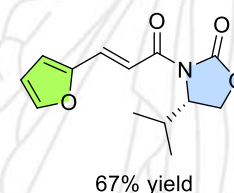
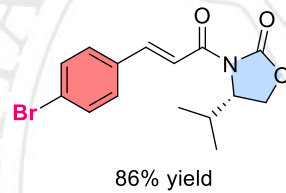
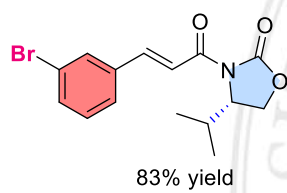
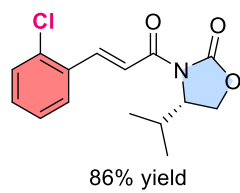
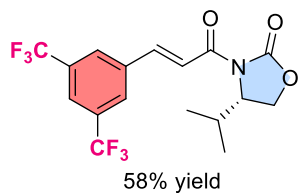
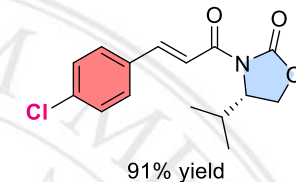
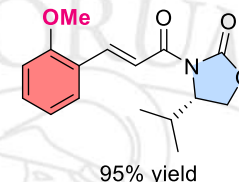
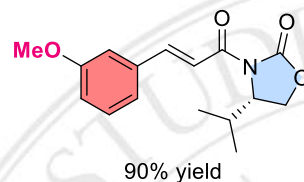
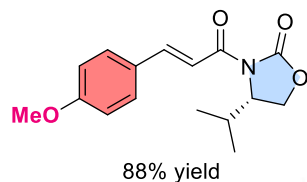
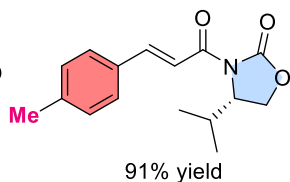
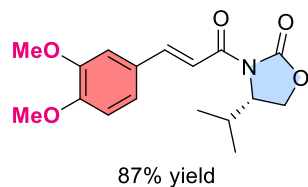
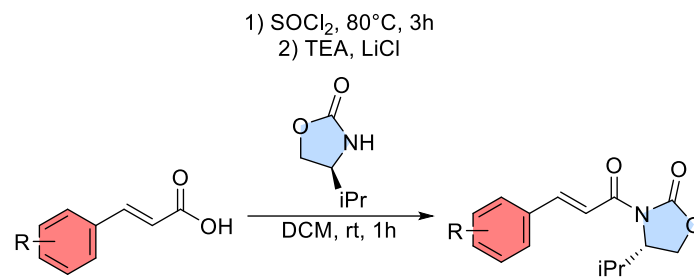


455 nm, 3,4 W/cm<sup>2</sup>



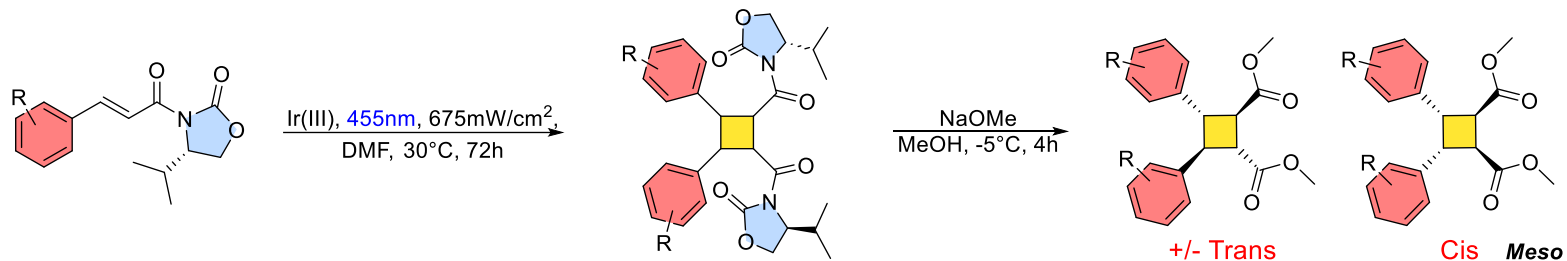


# Reaction Scope: Substrates synthesis

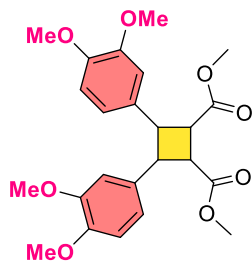




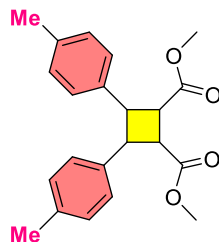
# SCOPE: Cyclisation & Deprotection



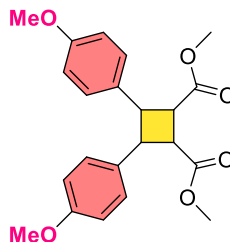
rapid filtration on silica gel



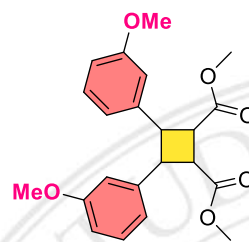
85% yield  
dr: 70:30



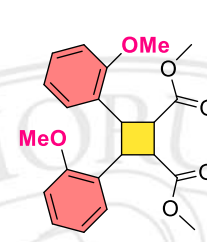
93% yield  
dr  $\geq 98:2$



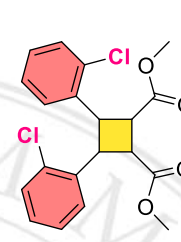
94% yield  
dr: 70:30



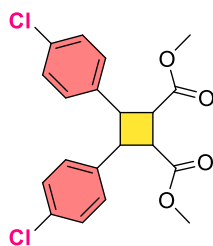
91% yield  
dr: 70:30



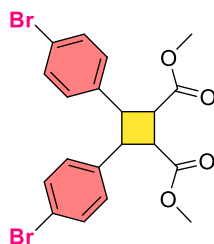
92% yield  
dr: 70:30



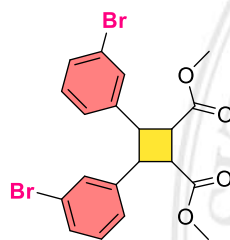
85% yield  
dr  $\geq 98:2$



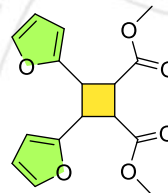
86% yield  
dr  $\geq 98:2$



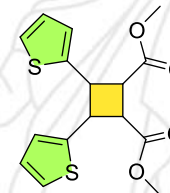
83% yield  
dr: 60:40



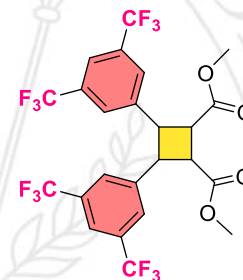
79% yield  
dr  $\geq 98:2$



90% yield  
dr: 50:50



89% yield  
dr: 50:50

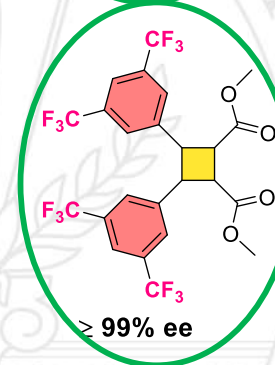
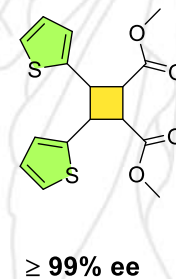
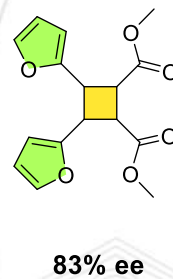
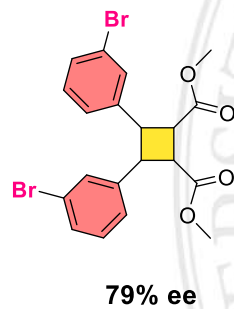
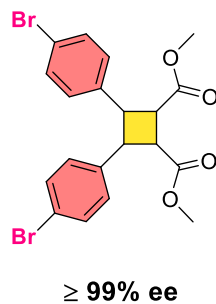
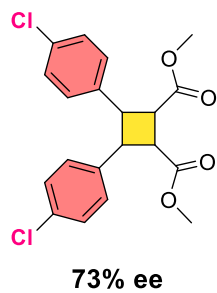
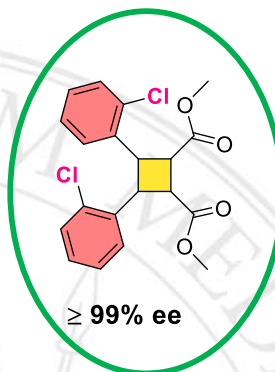
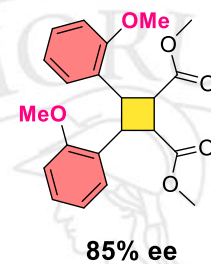
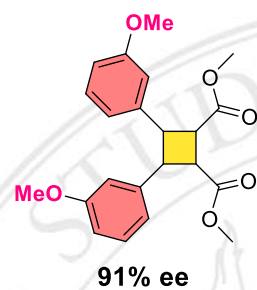
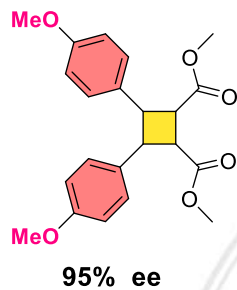
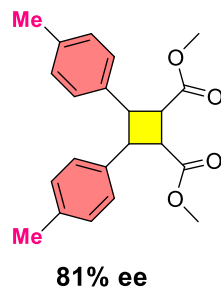
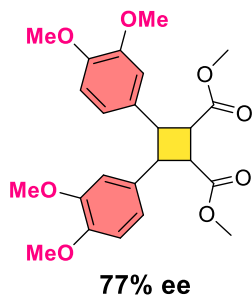
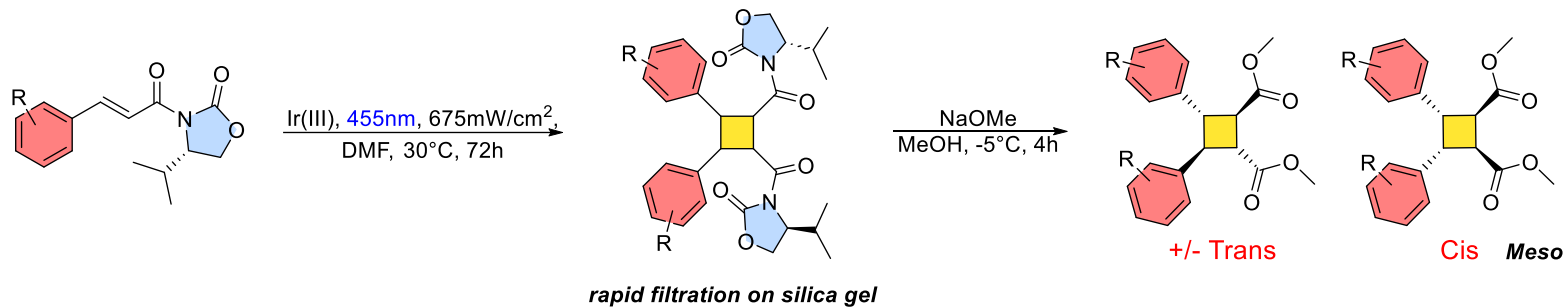


92% yield  
dr  $\geq 98:2$



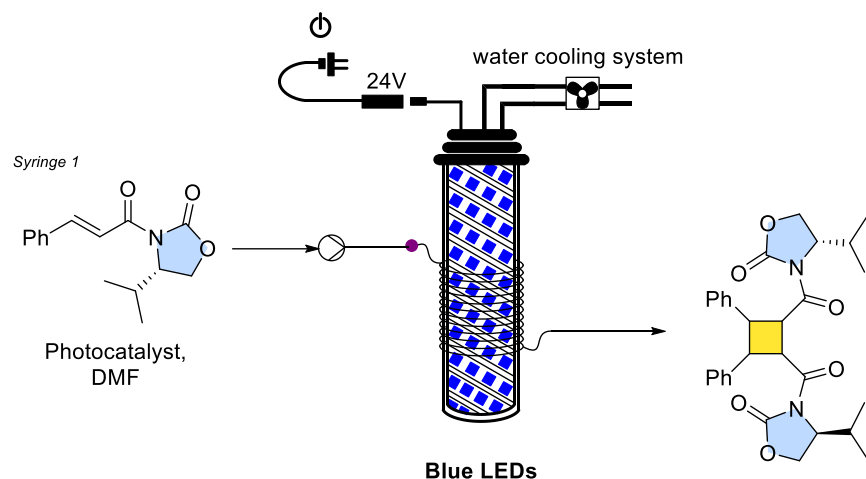


# Enantioselectivity

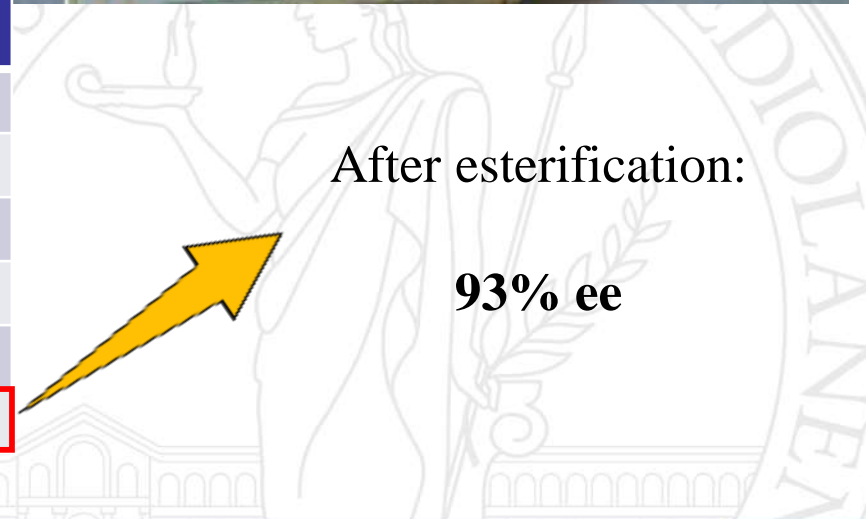




# Flow Chemistry: Product Intensification



Entry	[M]	Residence Time	NMR yield <sup>a</sup>
1	0.5 M	30 min	<5%
2	0.5 M	60 min	43%
3	2 M	30 min	41%
4	2 M	60 min	73%
5	4 M	30 min	43%
6	4 M	60 min	88%



After esterification:

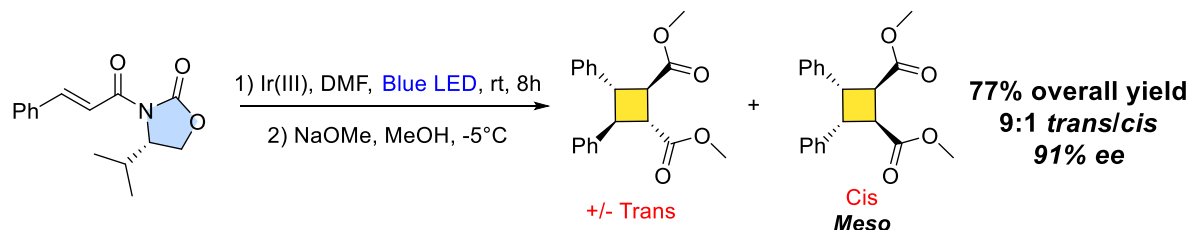
93% ee

<sup>a</sup> 1,3,5-trimethoxybenzene as internal standard



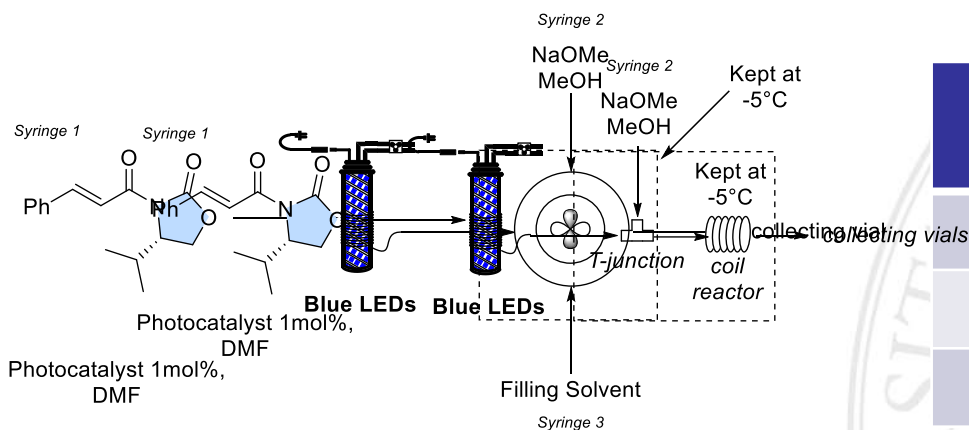


# One Pot Reaction in Batch



## In Flow Telescoped Process

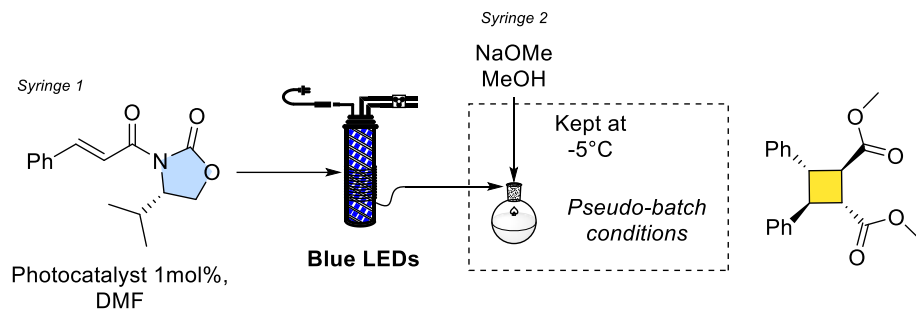
### Setup II: Coil-Coil Reactor



Filling Solvent	NaOMe eq.	Output
Hexane	2,1	<b>Clogging!!</b> clogging
Methanol	2,1	<5%
Methanol	7	35%; 77% ee



# Setup III: in Continuo Two-Step Flow/Batch Reaction



Residence time of 1h  
+ 1h for deprotection.

**72% yield**  
**87% ee**





# Productivity and Space-Time-Yield

- Productivity: amount of generated product per time
- Space-time-yield: amount of generated product per volume per time

Method	Productivity <sup>a</sup> [mmol/h]	Rel. Factor	STY <sup>b</sup> [mmol/mL*h]	Rel. Factor
Batch	$3,7 \times 10^{-2}$	1	$4,8 \times 10^{-2}$	1
Flow	$2,1 \times 10^{-1}$	5,8	3,52	73

<sup>a</sup> **Productivity:** moles of product (calculated from isolated yield) divided by the time required to collect the product obtained by the reaction of 0,38 mmol of starting material

<sup>b</sup> **Space-time-yield:** moles of product in reactor, divided by residence time and reactor volume

Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* 2017, 117 (18), 11796-11893.





# Conclusions

- Successful implementation of a diastereoselective [2+2] photocyclisation of cinnamates
- Up to 99% enantioselectivity in the synthesis of cyclobutane derivatives
- Synthesis of a library of enantioenriched products with different electronic and steric properties
- Development of an efficient in-flow protocol
- Enhanced productivity and space-time-yield in the in-flow process

## Work Published:

- Medici, F.; Puglisi, A.; Rossi, S.; Raimondi, L.; Benaglia, M. Stereoselective [2 + 2] Photodimerization: A Viable Strategy for the Synthesis of Enantiopure Cyclobutane Derivatives. *Org. Biomol. Chem.* **2023**, *21* (14), 2899-2904.

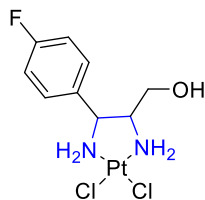




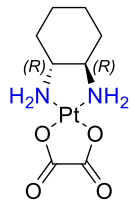
# Electrochemical Stereoselective Pinacol Coupling: an Easy Access to Chiral Diamines

## 1,2-Diamines in Everyday Life

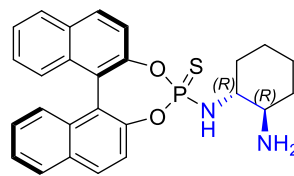
### 1,2-diamines



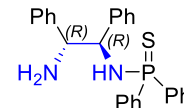
Anticancer candidate



Oxaliplatin anticancer

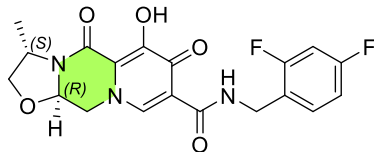


anti-viral candidate

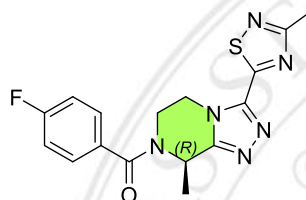


anti-fungine candidate

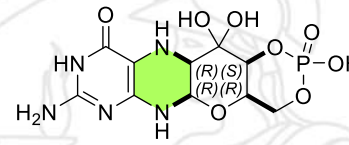
### Piperazine derivatives



Cabotegravir  
Treatment of HIV infection



Fezolinetant  
Menopause hot flashes treatment



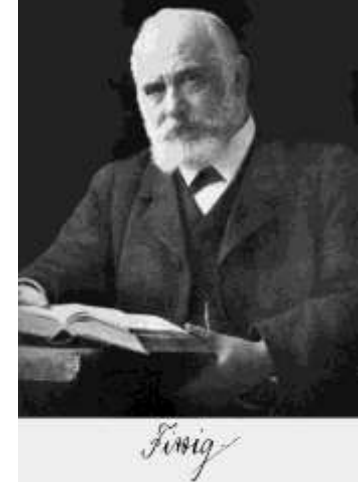
Fosdenopterin  
Treatment of Molybdenum cofactor deficiency type A

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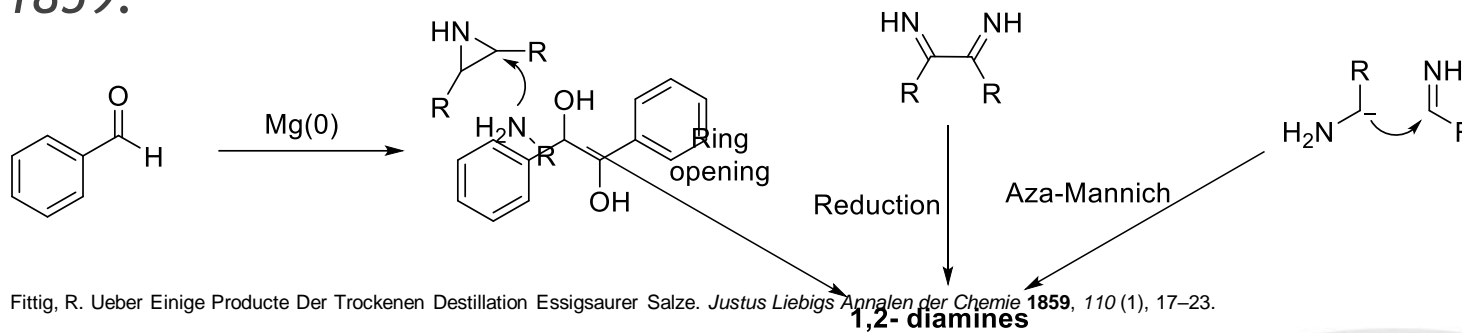




# 1,2-Diamines Background



Pinacol-coupling was discovered by Wilhelm Rudolph Fittig in 1859.



Fittig, R. Ueber Einige Producte Der Trockenen Destillation Essigsaurer Salze. *Justus Liebigs Annalen der Chemie* **1859**, 110 (1), 17–23.

1,2-diamines

Amination

Aza-Pinacol

The **Aza-Pinacol** coupling



Anselmino, O. Reduktionsprodukte Schiffscher Basen. *Berichte der deutschen chemischen Gesellschaft* **1908**, 41 (1), 621–623.

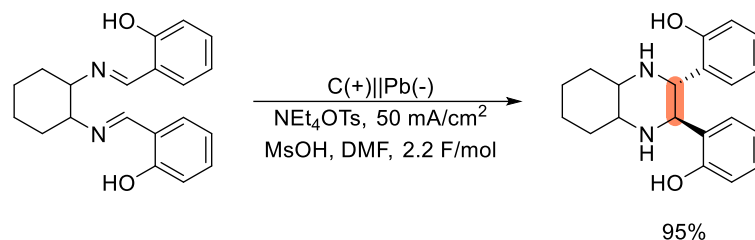
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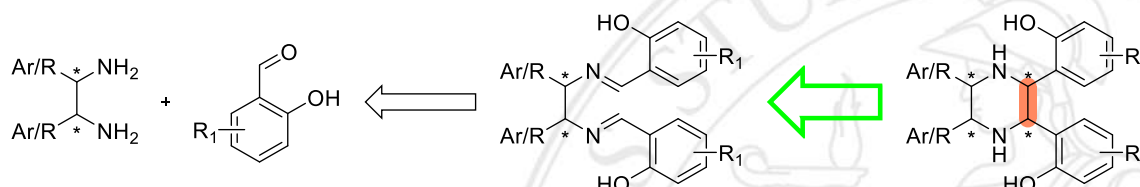


# Aim of the Project

## Electrosynthesis of a tetra-substituted piperazine as chiral scaffold



Shono, T.; Kise, N.; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *Electroorganic Chemistry*. 129. Electroreductive Synthesis of Chiral Piperazines and Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of the Chiral Piperazines. *J. Org. Chem.* **1991**, *56* (9), 3063-3067.



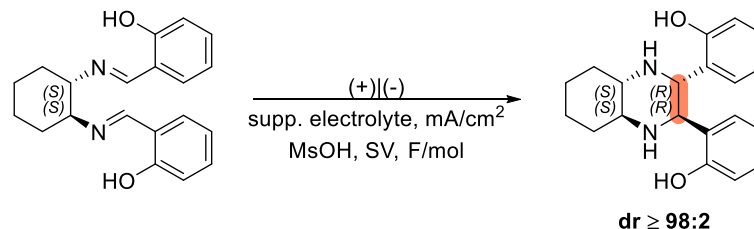
*Easier Conditions  
Increasing of the Scope*

*Carry Out the reaction  
Under Flow Conditions*





# Reaction Optimisation



	Cathode	Anode	Supp. Electr.	Eq.	J(mA/cm <sup>2</sup> )	Solvent	F/mol	Yield %
1	Pt	Pt	NEt <sub>4</sub> BF <sub>4</sub>	2,6	2,5	ACN	2,2	51
2	Pt	Gf	NEt <sub>4</sub> BF <sub>4</sub>	2,6	2,5	DMF	2,2	64
3	Pt	Zn	NEt <sub>4</sub> BF <sub>4</sub>	2,6	2,5	DMF	2,5	61
4	Pt	Zn	NEt <sub>4</sub> BF <sub>4</sub>	2,6	2,5	DMF	2,2	64
5	Pt	Pt	NEt <sub>4</sub> BF <sub>4</sub>	2,6	2,5	DMF	2,2	68
6	SS	SS	NEt <sub>4</sub> BF <sub>4</sub>	2,6	2,5	DMF	2,2	47
7	GC	GC	NEt <sub>4</sub> BF <sub>4</sub>	2,6	2,5	DMF	2,2	85
8	GC	GC	NEt <sub>4</sub> BF <sub>4</sub>	1,3	2,5	DMF	2,2	50
9	GC	GC	NEt <sub>4</sub> BF <sub>4</sub>	2,6	5	DMF	2,2	56
10	GC	GC	NBu <sub>4</sub> BF <sub>4</sub>	2,6	5	DMF	2,2	47

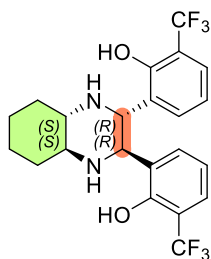
Gf: Graphite; SS: Stainless Steel; GC: Glassy Carbon

Paper submitted

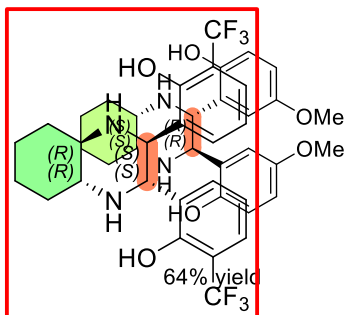




# Reaction Scope



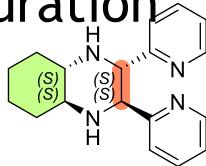
68% yield



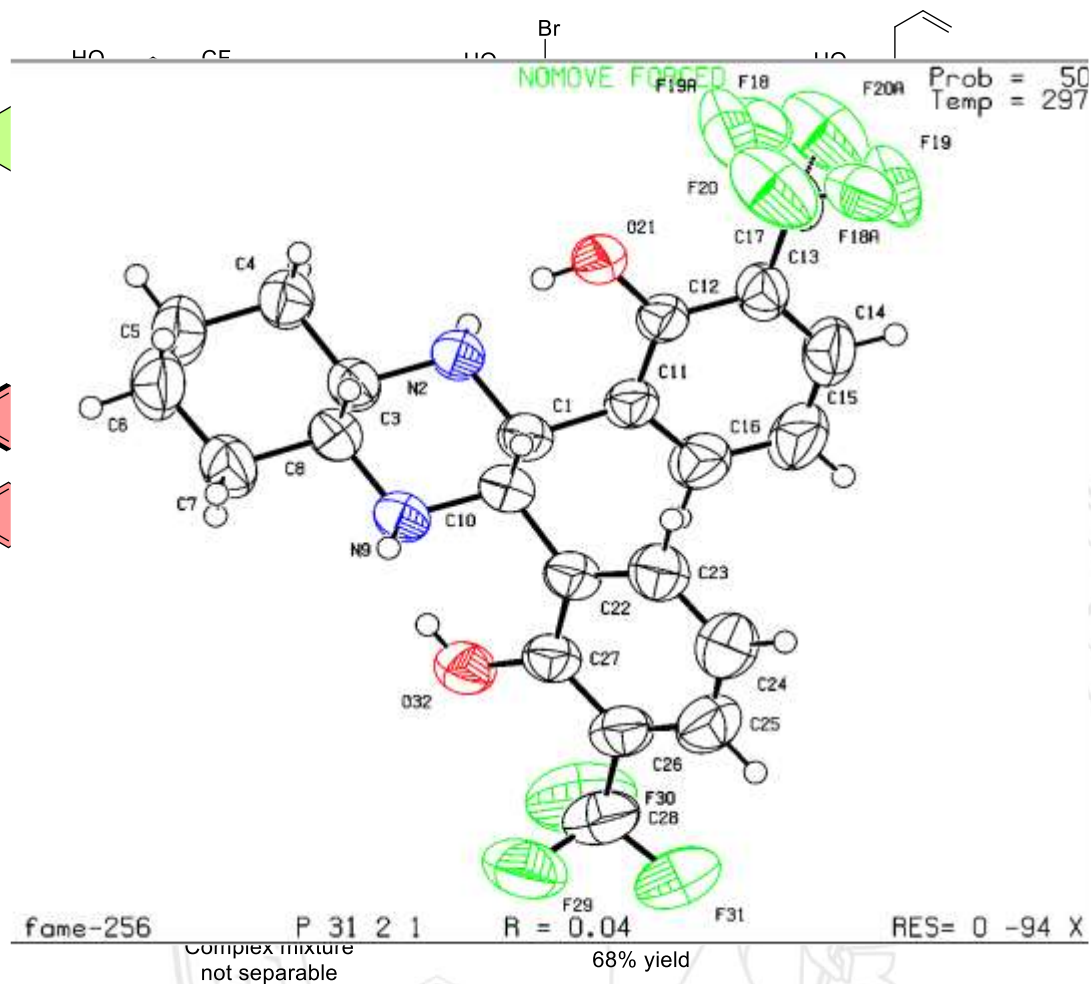
64% yield

## Absolute Configuration

CCDC number: 2430018



Degradation



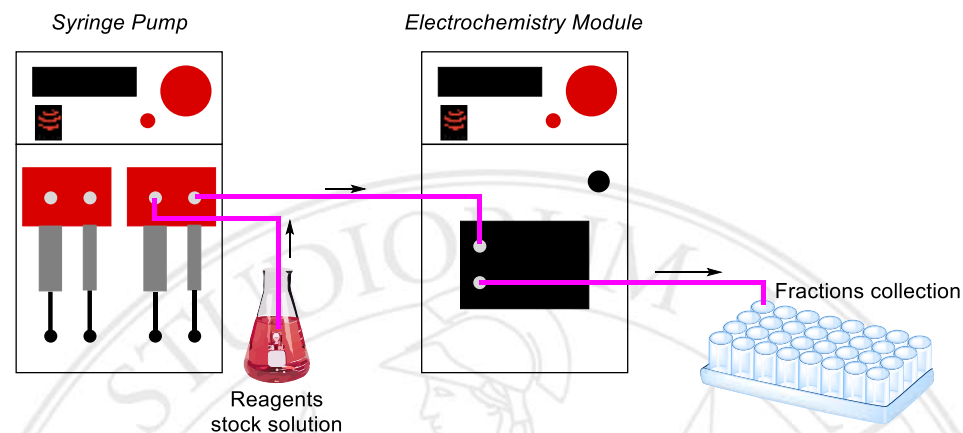
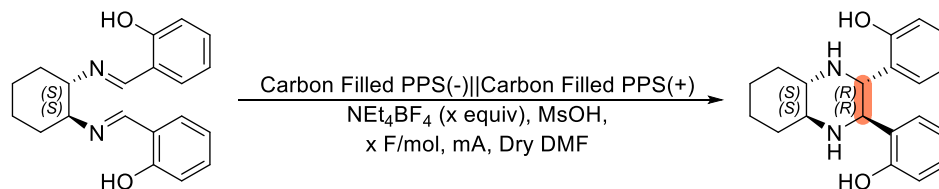
Thanks to Prof. Leonardo Lo Presti, University of Milan, for the structure resolution and absolute configuration.

Paper submitted





# In-Flow Reaction



$$Q = \frac{I}{V \cdot c \cdot F}$$

Q: Amount of charge (F/mol)

I: Current intensity (A)

V: Flow rate (mL/min)

c: Concentration [M]

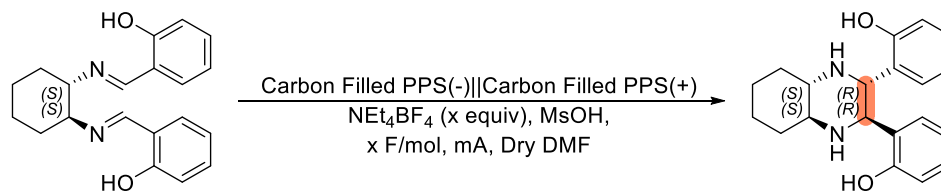
F: Faraday constant (1608.0889 minA/mol)

Paper submitted





# In-Flow Reaction



	mA	Flow rate (μL/min)	Residence Time (min)	F/mol	NEt <sub>4</sub> BF <sub>4</sub> eq.	NMR yield (%) <sup>a</sup>	Productivity (mmol/h)	R. Factor <sup>b</sup>	STY (mmol/mLh)	R. Factor <sup>b</sup>
1	5	10	22,5	2,2	2,6	22	0,01650	0,27	0,07333	4,83
2	20	40	5,63	2,2	2,6	9	0,02700	0,044	0,12097	7,97
3	80	160	1,41	2,2	2,6	20	0,24000	3,95	0,53191	35,04
4	20	40	5,63	2,2	1,3	28	0,08400	1,38	0,37634	24,79
5	40	80	2,82	2,2	1,3	26	0,15600	2,57	0,69149	45,56
6	5	6	37,5	4,15	1,3	94	0,04230	0,70	0,18800	12,39
7	80	96	2,34	4,15	1,3	56	0,40320	6,64	1,79487	118,25

<sup>a</sup> 1,3,5-Trimethoxybenzene as internal standard

<sup>b</sup> Compared to the value of the batch reaction: Productivity: 0,06071; STY: 0,01518

Paper submitted





# Conclusion & Perspective

- Optimisation of the electrochemical protocol for the synthesis of chiral diamines
- Different imines have been employed as substrates, leading to the formation of the desired product in up to 75% yield
- A single diastereoisomer was obtained
- An in-flow protocol of the electrochemical stereoselective pinacol coupling has been developed

*Paper Submitted*



# Final Thanks



The authors thank MUSA-Multilayered Urban Sustainability Action-project, funded by the European Union-NextGenerationEU, under the National Recovery and Resilience Plan (NRRP) Mission 4 Component 2 Investment Line 1.5: Strengthening of research structures and creation of R&D “innovation ecosystems”, set up of “territorial leaders in R&D”.

Prof. Maurizio Benaglia, Prof. Laura Raimondi, Prof. Alessandra Puglisi, Prof. Sergio Rossi, Dr. Valerio Chirolì, Dr. Francesca Franco

And all the Benaglia group.

