UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI CHIMICA

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

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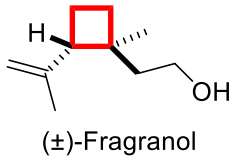
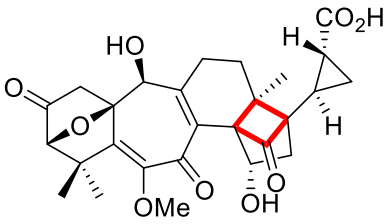
Università degli Studi di Palermo
XL CO CD
PALERMO 11-15 settembre 2022
XL Convegno Nazionale della Divisione di Chimica Organica della Società Chimica Italiana
Società Chimica Italiana Divisione di Chimica Organica

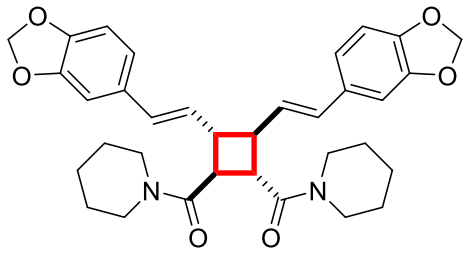
CYCLOBUTANES IN NATURE



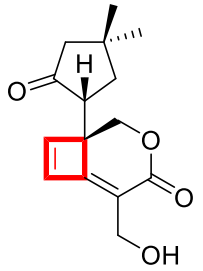
(±)-Fragranol



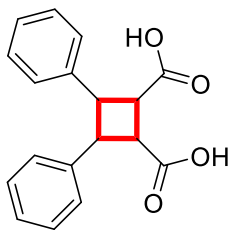
Solanoeclepin A



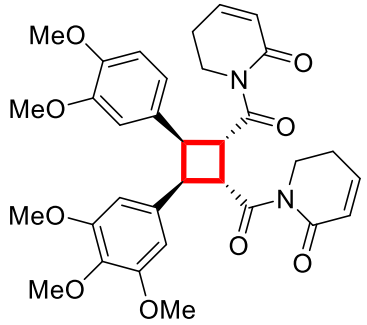
(±)-Nigramide



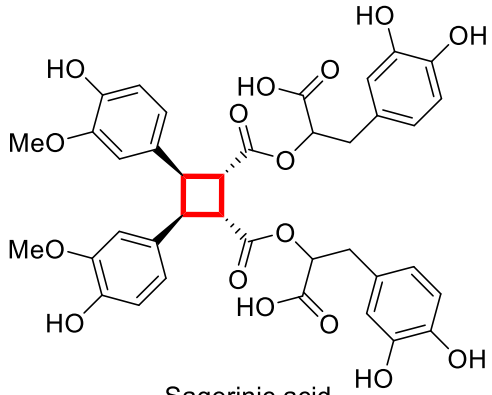
(+)- Fomannosin



Truxinic acid



Piperarborenine D

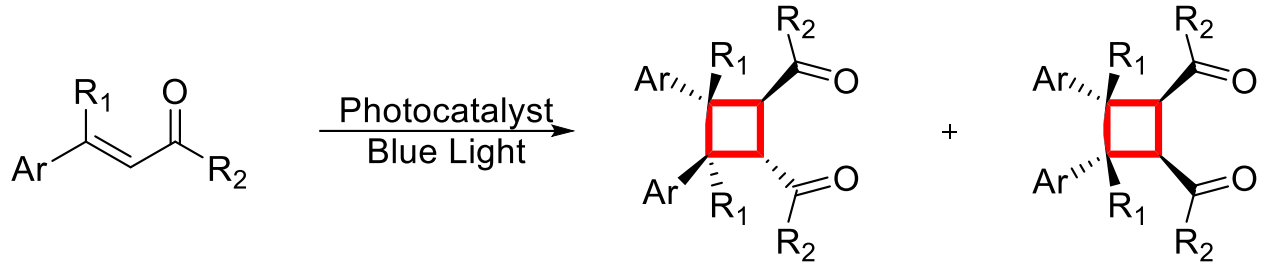


Sagerinic acid

[2+2] cycloaddition from cinnamic derivatives

Li, J.; Gao, K.; Bian, M.; Ding, H., *Org. Chem. Front.* **2019**, *7* (1), 136–154.

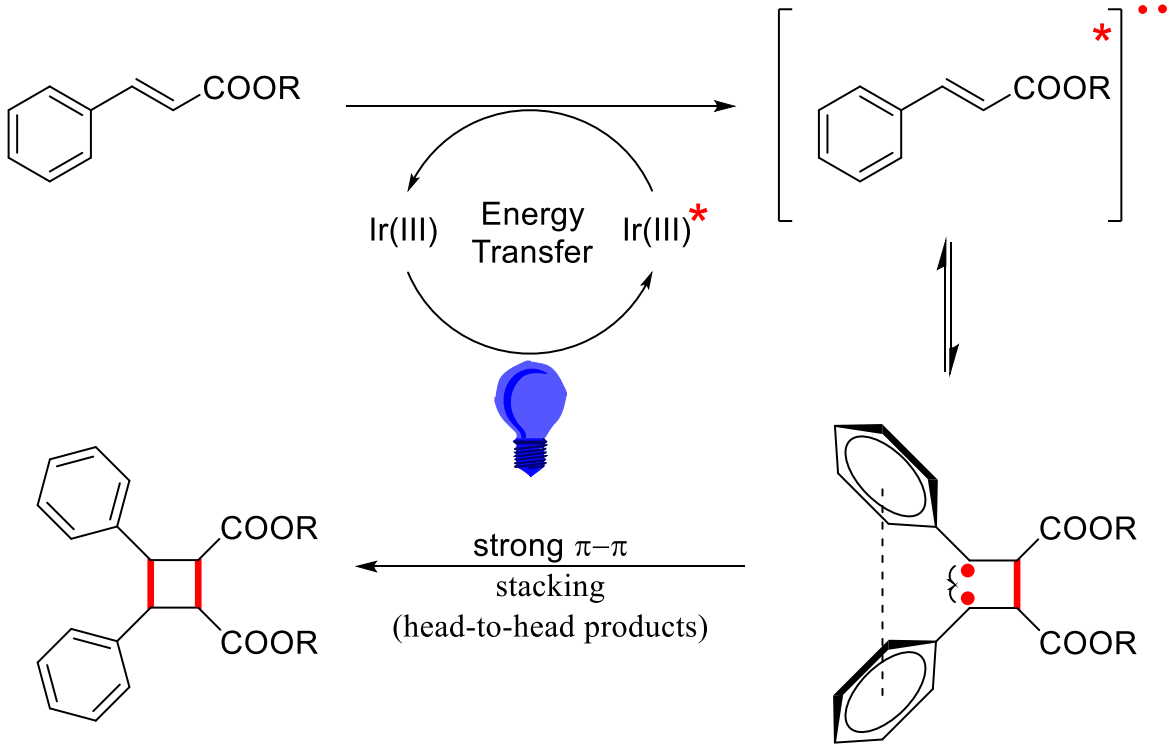
BACKGROUND

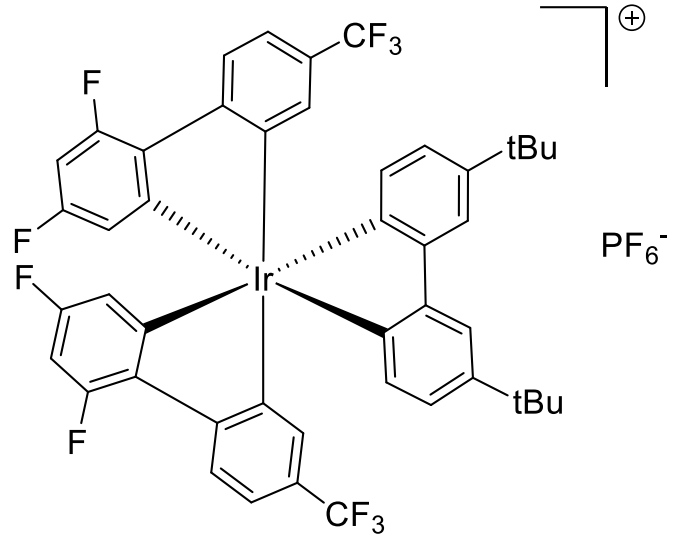


***trans*-Isomer** ***cis*-Isomer**

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

For Cinnamic Esters



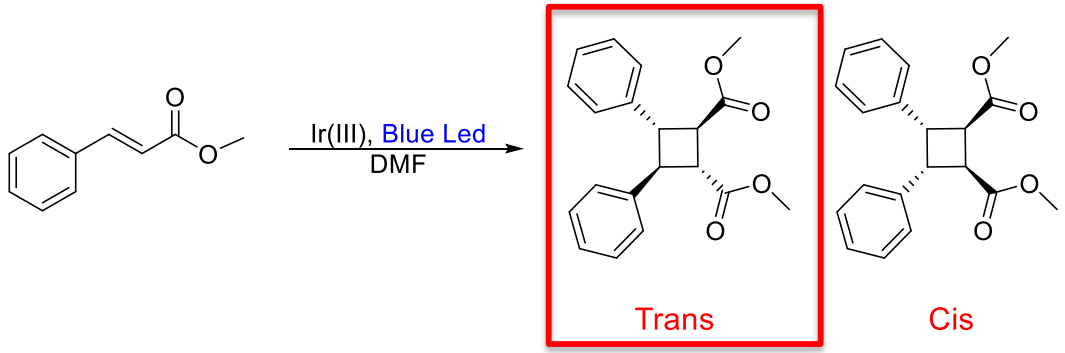


Ir(III)*/Ir(II)= 1,21V
Ir(III)*/Ir(IV)= -0,89V
Ir(III)/Ir(II)= -1,37V
Ir(IV)/Ir(III)= 1,69V
Ir(III)*= 2300 ns

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

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

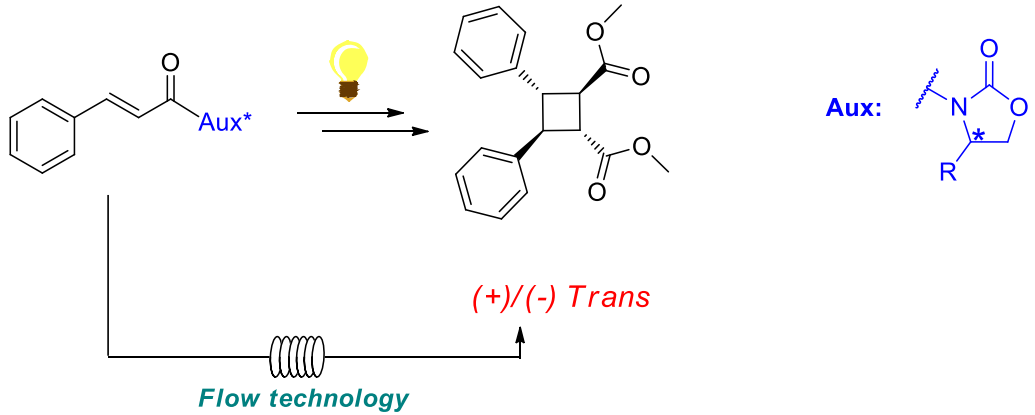
PROJECT OBJECTIVE



Control of the ABSOLUTE stereochemistry of the product

No chiral catalyst known, to the best of our knowledge, for the cyclisation of cinnamates

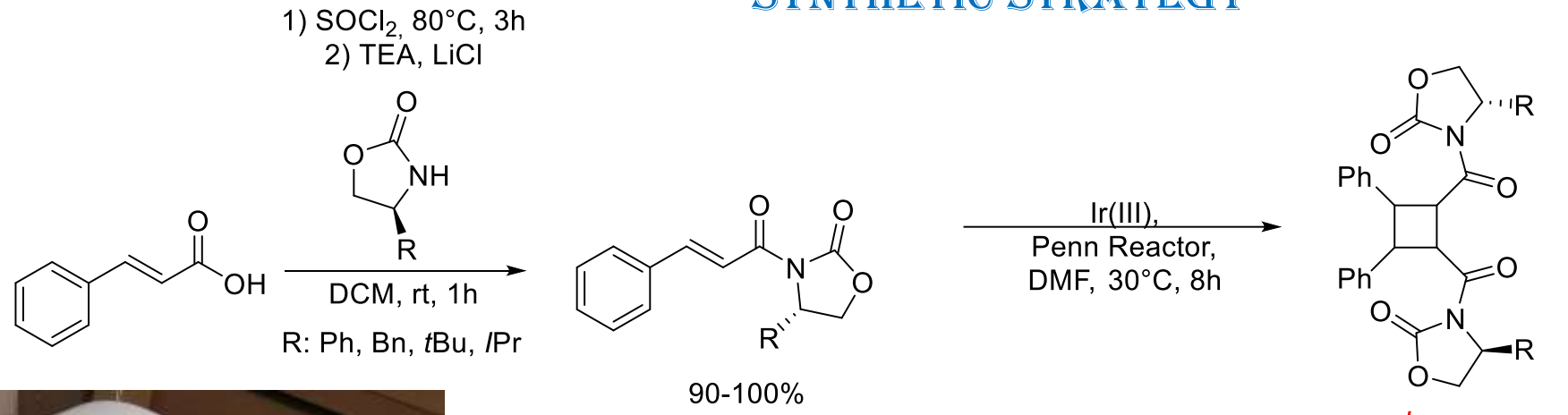
Introduction of a chiral auxiliary in the molecule



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.

For a review on chiral auxiliaries: 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***-tBu: 71% yield
- ***S***-Bn: 58% yield
- ***S***-Ph: 73% yield
- ***S***-iPr: 68% yield

455 nm, 3,4 W/cm^2

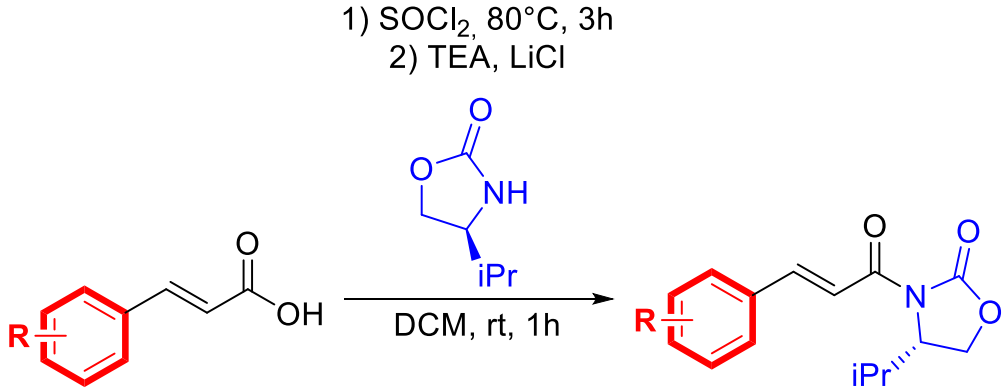
R:

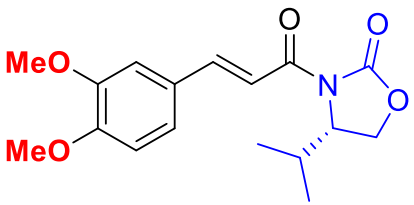
- ***S***-tBu: 79% ee
- ***S***-Bn: 67% ee
- ***S***-Ph: 71% ee
- ***S***-iPr: 93% ee;

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

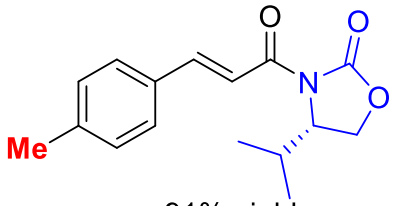
Green, B. S.; Hagler, A. T.; Rabinsohn, Y.; Rejtõ, M. *Israel Journal of Chemistry* **1976**, *15* (1–2), 124–130.

REACTION SCOPE: SUBSTRATES SYNTHESIS

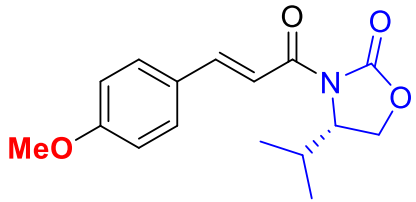




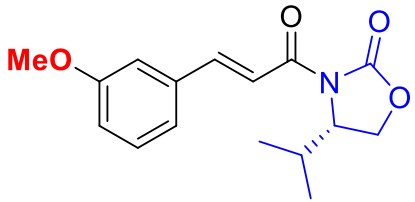
87% yield



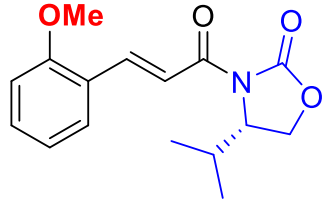
91% yield



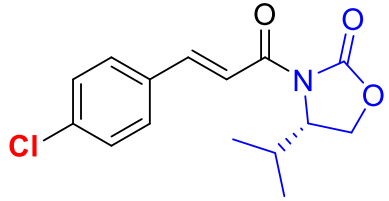
88% yield



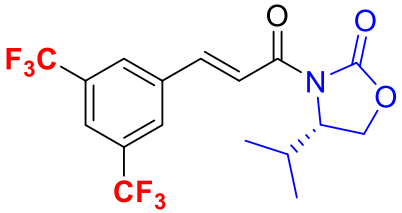
90% yield



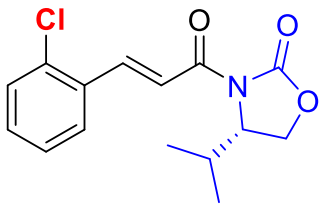
95% yield



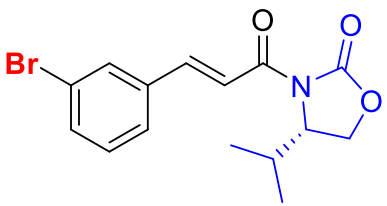
91% yield



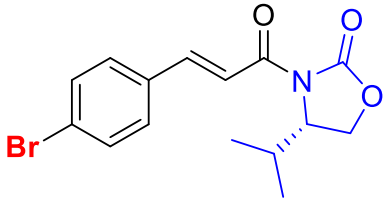
58% yield



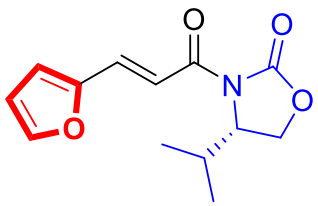
86% yield



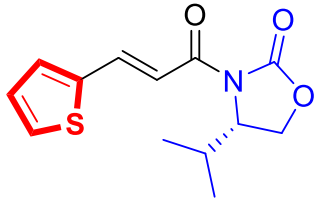
83% yield



86% yield

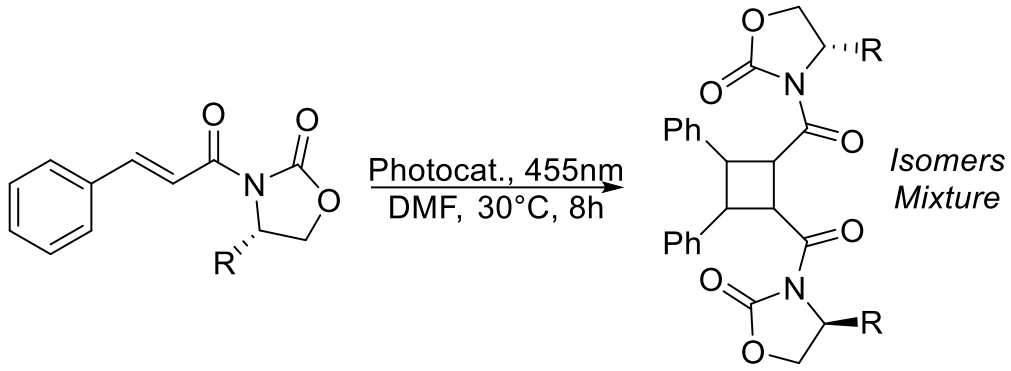


67% yield



71% yield

IN PARALLEL PHOTOCATALYSED REACTIONS



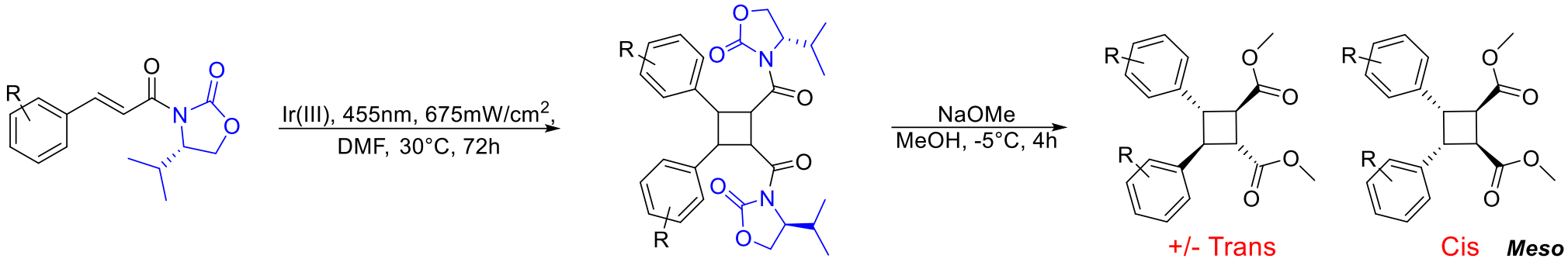
Investigation on multi-vials photoreactors

LED: 12V, 8.18 mW/cm^2, blue led (25 cm stripe)

LED: 24V, 674 mW/cm^2, blue led (30 cm stripe)

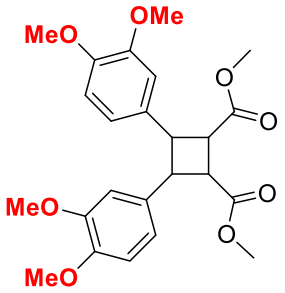
Rossi, S.; Dozzi, M. V.; Puglisi, A.; Pagani, M. *Chemistry Teacher International* **2020**, *2* (2).

SCOPE: CYCLISATION & DEPROTECTION

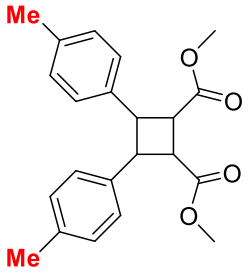


rapid filtration on silica gel

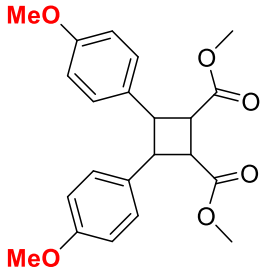
dr *trans/cis* from 50:50 to 98:2



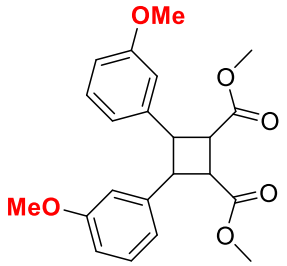
85% yield
dr: 70:30



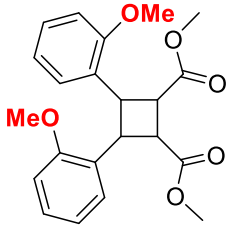
93% yield
dr ≥ 98:2



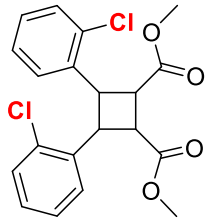
94% yield
dr: 70:30



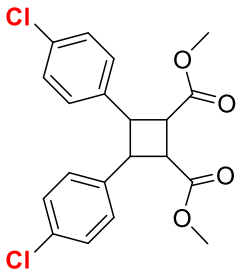
91% yield
dr: 70:30



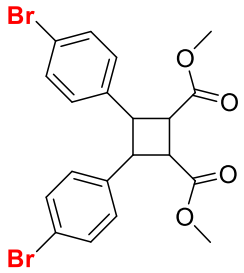
92% yield
dr: 70:30



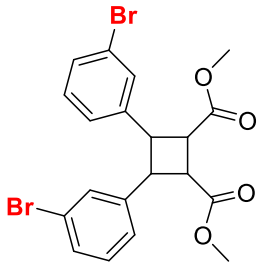
85% yield
dr ≥ 98:2



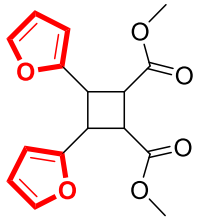
86% yield
dr ≥ 98:2



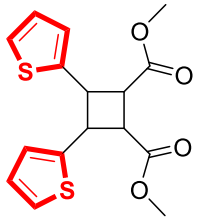
83% yield
dr: 60:40



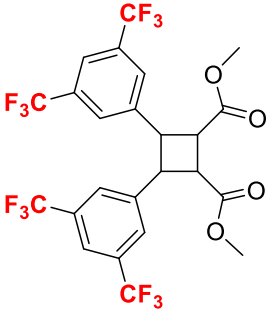
79% yield
dr ≥ 98:2



90% yield
dr: 50:50

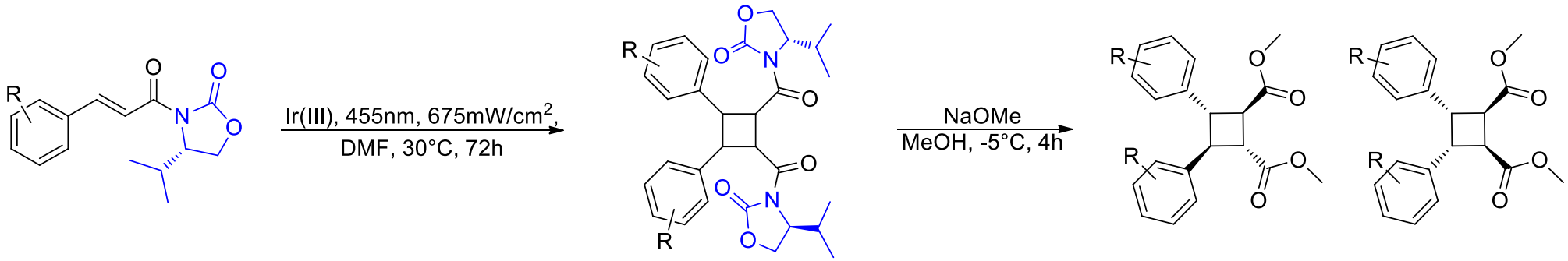


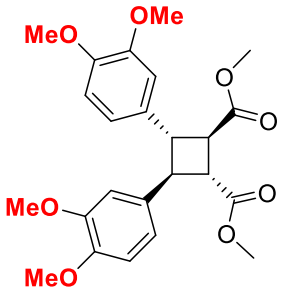
89% yield
dr: 50:50



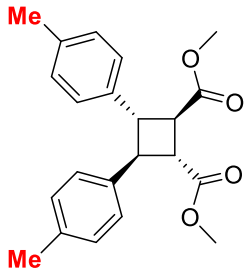
92% yield
dr ≥ 98:2

ENANTIOSELECTIVITY

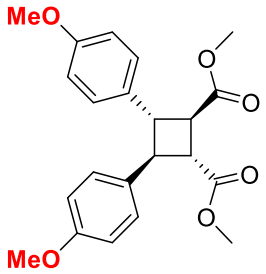




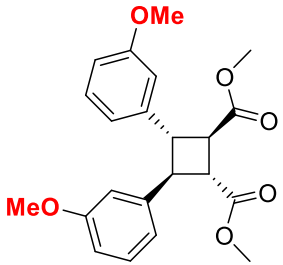
77% ee;
α_D^{20}: -4.00



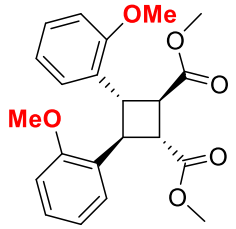
81% ee



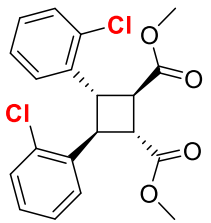
95% ee



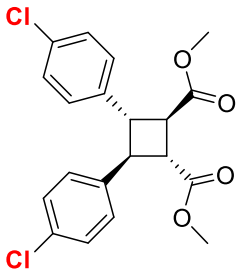
91% ee



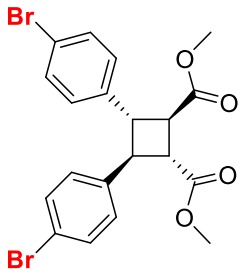
85% ee



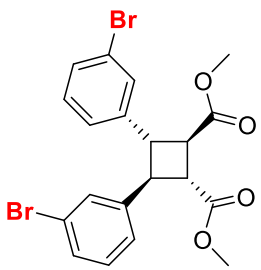
≥ 99% ee
α_D^{20}: -6.67



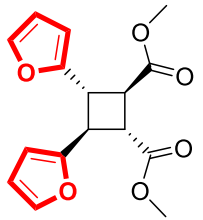
73% ee;
α_D^{20}: -22.50



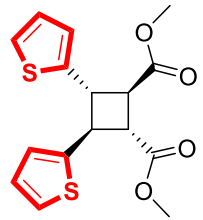
≥ 99% ee



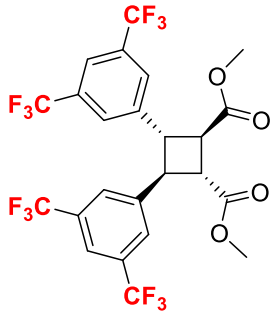
79% ee



83% ee



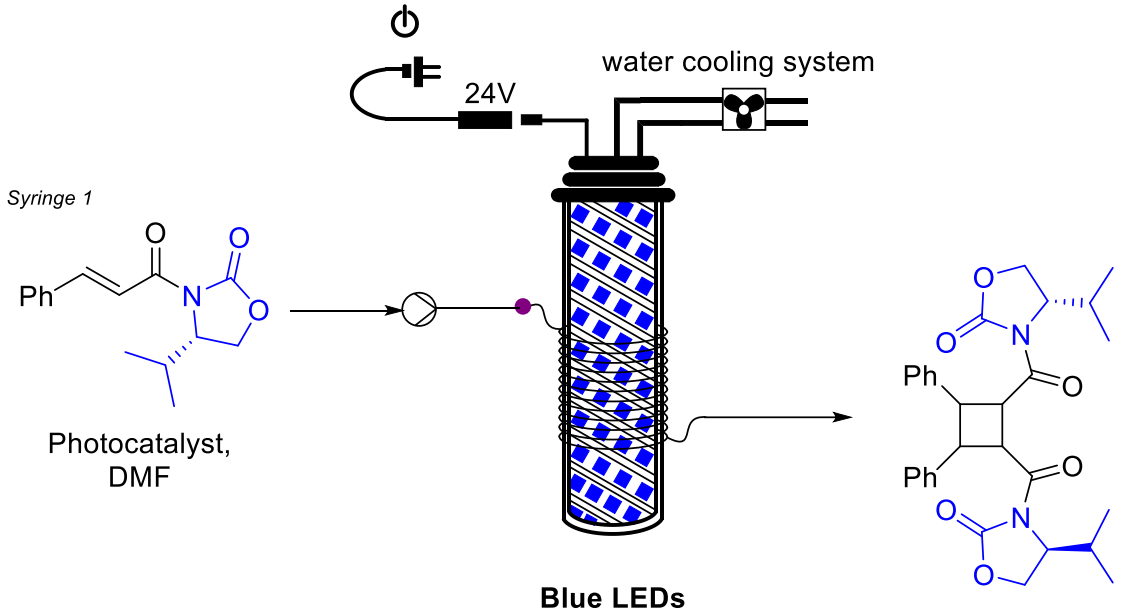
≥ 99% ee



≥ 99% ee;
α_D^{20}: +103.33

A greener and faster methodology

Dallinger, D.; Kappe, C. O., *Current Opinion in Green and Sustainable Chemistry* **2017**, *7*, 6–12.



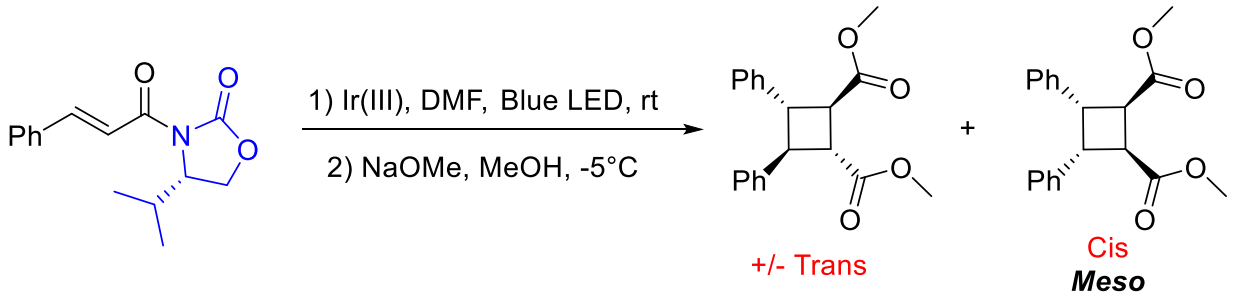
Entry	Concentration	Residence Time	NMR yield[a]
1	0.5 M	30 min	<5%
2	0.5 M	60 min	43%
3	2 M	30 min	41%
4	2 M	60 min	73%
5	4 M	30 min	43%
6	4 M	60 min	88%

[a] 1,3,5-trimethoxybenzene as internal standard

After esterification:

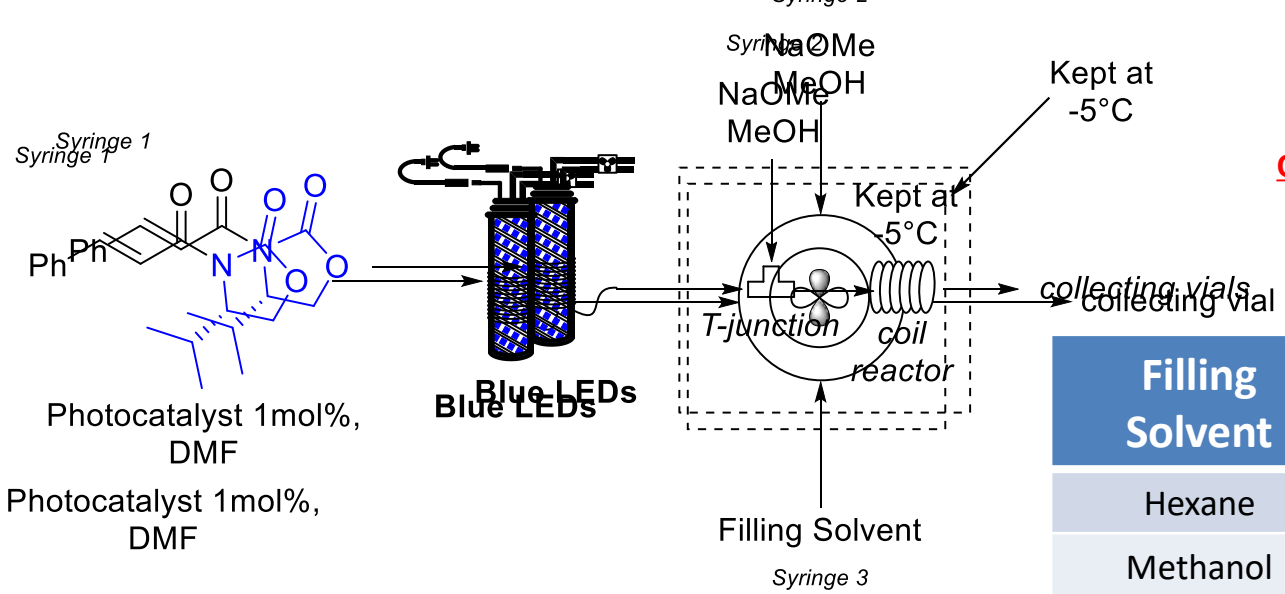
93% ee

ONE POT REACTION



77% overall yield
9:1 *trans*/*cis*

FLOW ARCHITECTURE: COIL REACTOR

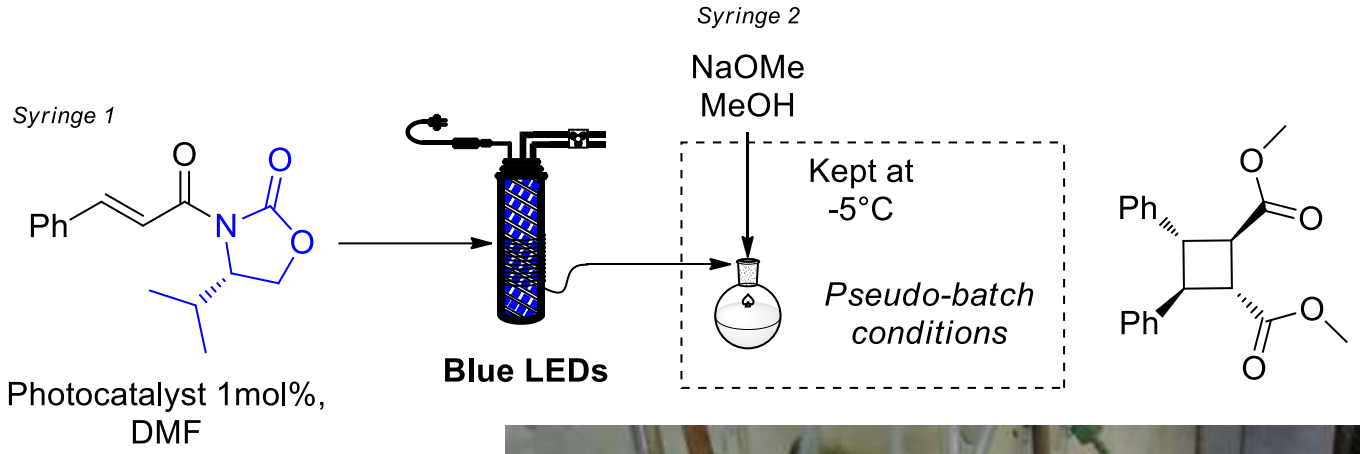


CSTR volume: 1,5 mL

Clogging

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

III FLOW ARCHITECTURE: IN CONTINUO TWO-STEP FLOW/BATCH REACTION



Collection time of 1h plus 1h of additional stirring.

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[a] [mmol/h]	Rel. Factor	STY[b] [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**

[a] **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

[b] **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 the space-time-yield in the in-flow process

Paper Submitted

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