Flow Photochemistry made easy in the advanced Vapourtec UV-150 Flow Photoreactor

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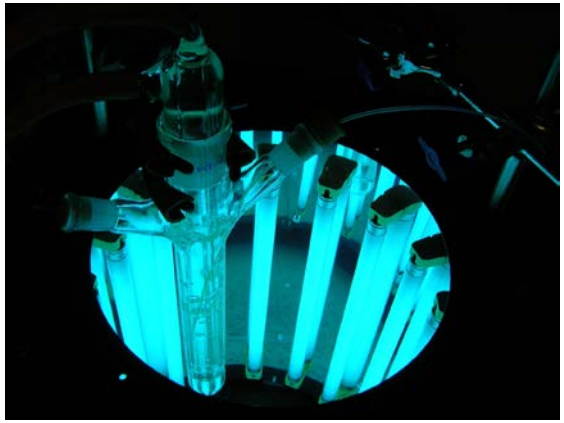
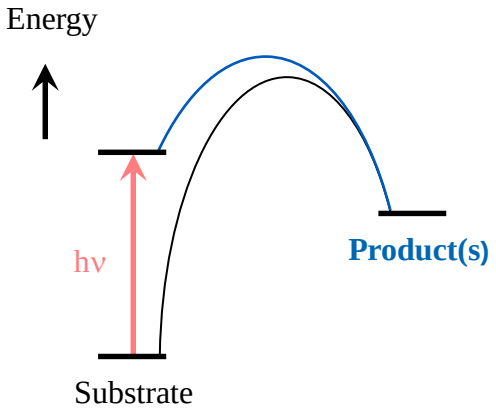
Continuous-flow Photochemistry

- Challenge: increasing need for new and unique lead structures.
- Approach: light activation to produce ‘exciting’ molecules.





N. Hoffmann *Chem. Rev.* **2008**, *108*, 1052.

- Advantages:
  - Selective excitation of chromophore.
  - Reaction control with ‘flick of a switch’.
  - Light as a ‘soft’, ‘traceless’, ‘cold’ and ‘green’ chemical reagent.
  - Easy access to high energy compounds such as strained rings.

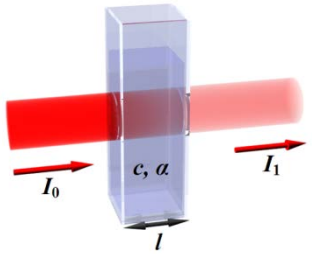
M. Oelgemöller *J. Chin. Chem. Soc.* **2014**, *61*, 743.

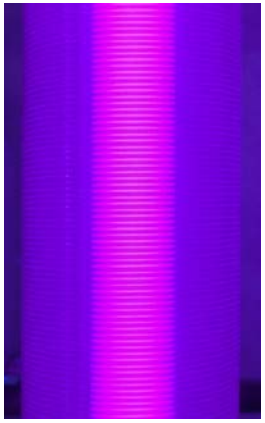
Continuous-flow Photochemistry

- Challenge: high dilution and common photodecompositions in batch.
- Approach: (micro)reactor in flow mode (microflow photochemistry).

Beer-Lambert Law

$A = -\log (I/I_0) = a \cdot c \cdot l$



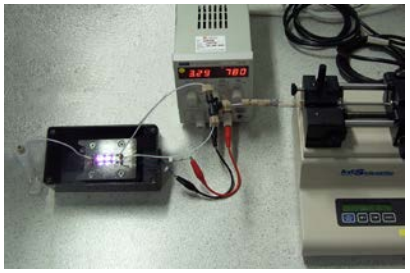


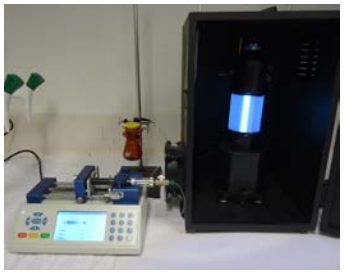
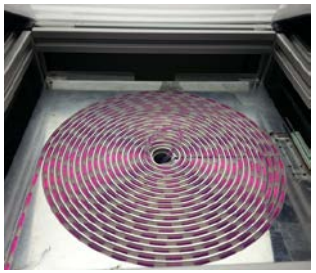
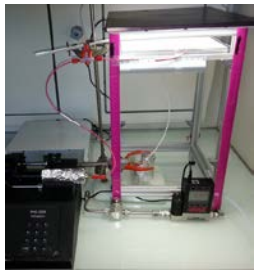
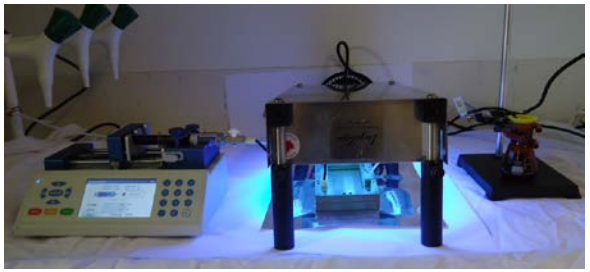
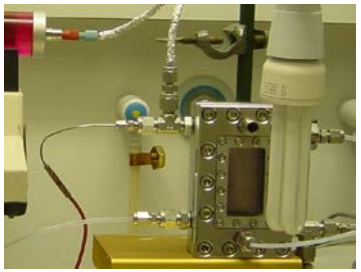
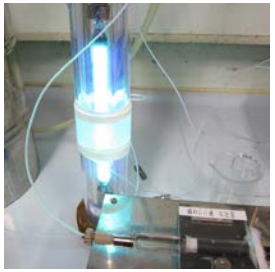
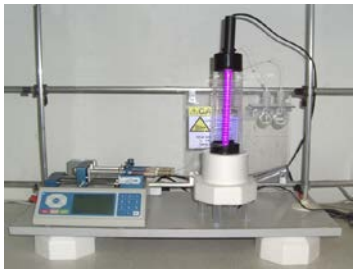
- Status and trends:
  - 'Proof of concept' using improvised reactors.
  - Safe manufacturing and 'taming of hazardous photoreactions'.
  - Parallel (library) synthesis and scale-up.
  - Application in medicinal and pharmaceutical chemistry.

M. Oelgemöller et al. *Photochem. Photobiol. Sci.* **2008**, *7*, 35; *Molecules* **2011**, *16*, 7522; *Chem. Eng. Technol.* **2012**, 1144.

Improvised Reactors

- Approach: usage of current photochemical and flow equipment.
- Technology trend: from embedded to capillary based reactors.



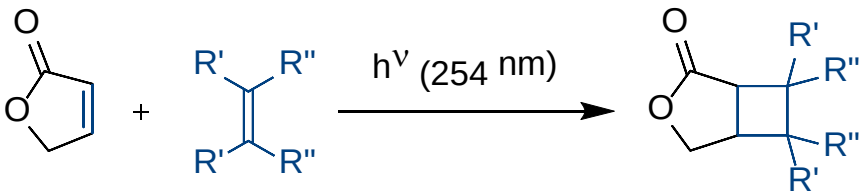








- Problems: poor matching of light sources and reaction channels.
- Needs:
  - Chemical Engineering and Reactor Modelling.
  - Dedicated purpose-designed reactor as ‘standard’.

K. Loubiere, M. Oelgemöller et al. *Chem. Eng. Proc.* **2016**, *104*, 120.

Examples

UVC – [2+2]-Photocycloadditions of Furanones

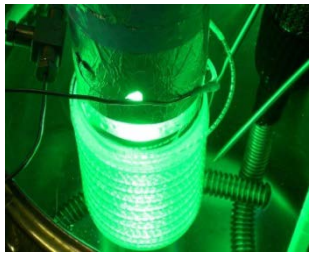


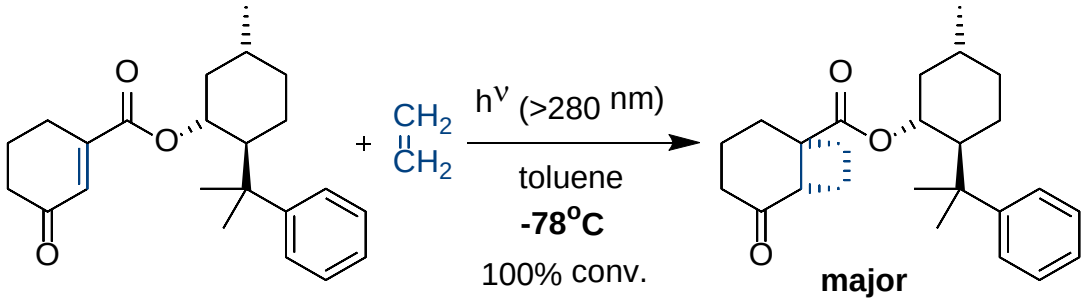
Conversions ‖ Yields

- batch: >95% ‖ 30/67% (>5 h)
- μ-reactor: >95% ‖ 43/65% (1.5 h)

Capillary Tower: FEP, 0.8 mm (ID), 10 m (L), 5 ml (V), 8 × 4 W (UVC)

UVB – Diastereodifferentiating [2+2]-Photocycloadditions



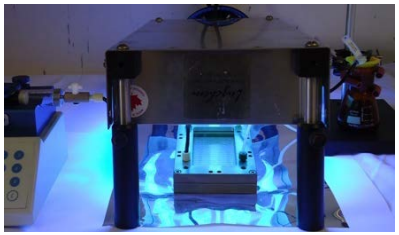


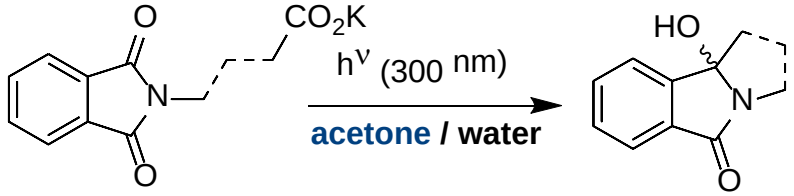
d.e.

- batch: 47% (15 min)
- μ-reactor: 52% (1 min)

Capillary Tower: FEP, 1 mm (ID), 1.5 m (L), 1.18 ml (V), 500 W (>200 nm)

UVB – Photodecarboxylations of Phthalimides





Conversions

- batch: 17-29% (60 min)
- μ-reactor: 72-100% (60 min)

Dwell device: 0.5 × 2 mm (D x W), 1.15 m (L), 1.68 ml (V), 5 × 8 W (UVB)

M. Oelgemöller et al. *Beilstein J. Org. Chem.* **2013**, *9*, 2015; *J. Flow. Chem.* **2012**, *2*, 73; *Org. Lett.* **2010**, *12*, 5170.

Vapourtec UV-150 Reactors

- Features:
  - Compact ‘plug & play’ module based on the R- and E-series.
  - Temperature control from -40°C to 80°C.
  - Flexible light-sources: low- and medium-pressure Hg, LEDs.
  - Precise control of exposure time (1 to 200 min for 10 ml coil).
  - Productivities of up to 15 grams of product per hour.
  - Possible tandem operation with thermal loop *in-series*.

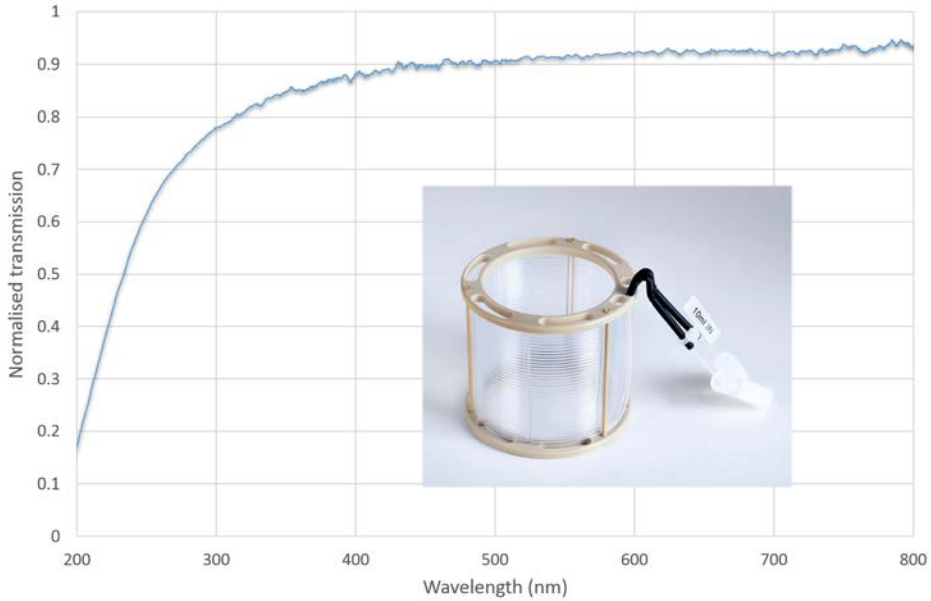
R-Series
piston pump
up to 42 bar
0.05-10 ml/min

E-Series
peristaltic pump
up to 10 bar
0.1-10 ml/min

Vapourtec Ltd (*https://www.vapourtec.com*).

Reactor Module

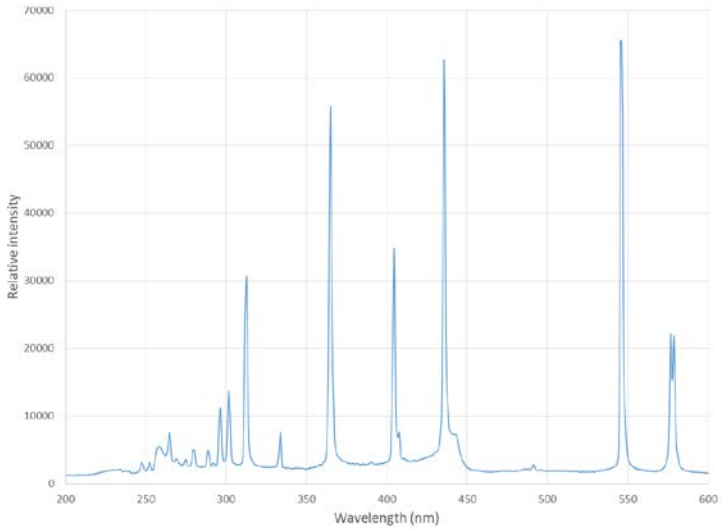
- Capillary coil:
  - Fluorinated Ethylene Propylene (FEP) with high (photo)-chemical stability and UV-transparency (ca. 65% at 250 nm).
  - Internal diameter: 1.3 mm; wall thickness: 0.15 mm.
  - Exchangeable reactor coils with 2 ml, 5 ml and 10 ml volume.
  - Safe, encapsulated design.



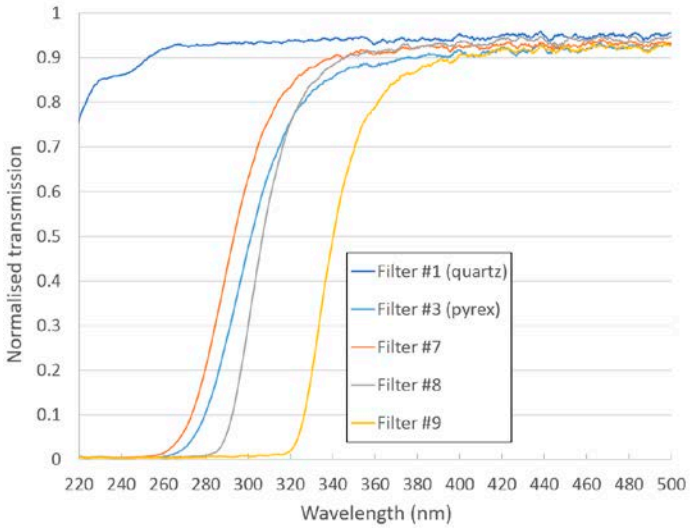
Vapourtec Ltd (*https://www.vapourtec.com*).

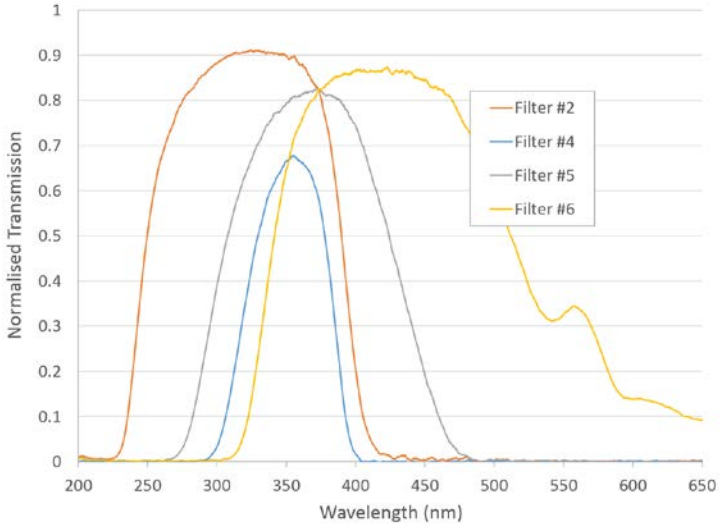
Light Sources

- Medium pressure Hg-lamp:
  - ‘Traditional’ light source.
  - Polychromatic (220-600 nm).
  - Dimmable from 75-150 W.



- Filter inserts:
  - Range of exchangeable 5 cut-off and 4 band-pass filters.



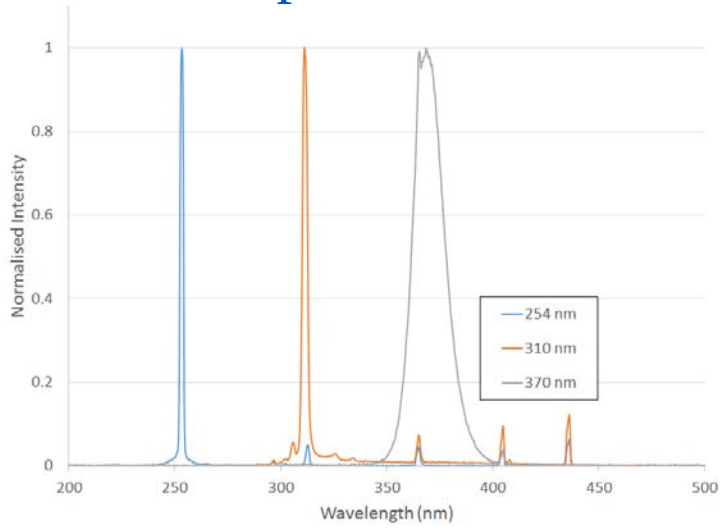


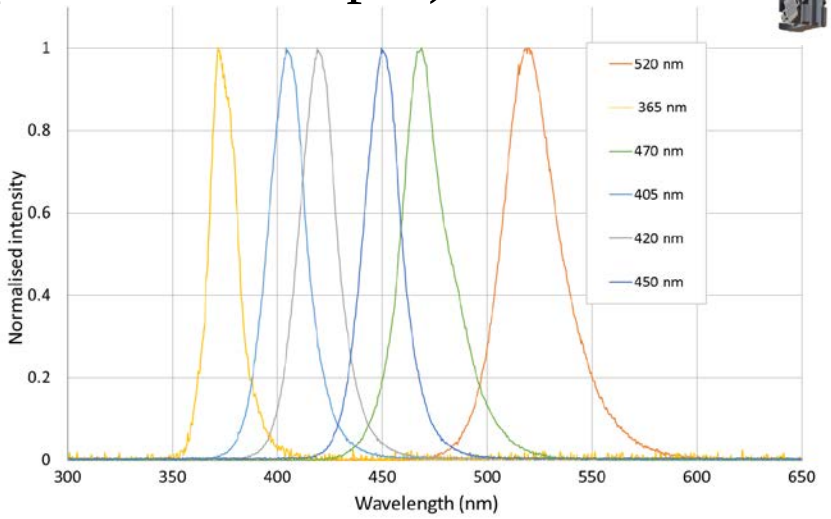
Vapourtec Ltd (*https://www.vapourtec.com*).

Light Sources

- Low pressure Hg-lamp:
  - 3 types (UVA, UVB, UVC) with low heat generation.
  - Radiant power of ca. 3 W (from 9 W input).

- LEDs:
  - 6 types of high-power LEDs (365-520 nm) with low heat generation.
  - Radiant power of ca. 3-24 W (from 60 W input).





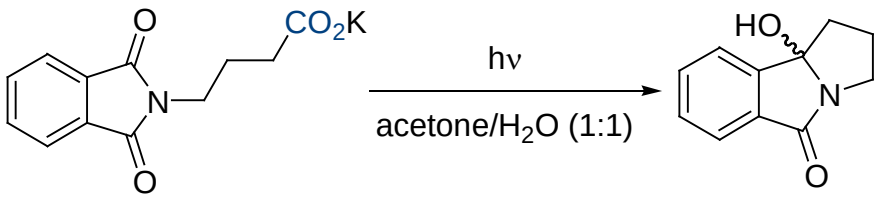
Vapourtec Ltd (*https://www.vapourtec.com*).

Photoreactions

- Approach:
  - Transfer of known batch reactions ‘from batch to flow’.
  - Process optimization (flow rates, concentrations, temperature, light source etc.).
  - Scalability.
- Photoreactions:
  - Photodecarboxylations.
  - [2+2] Photocycloadditions.
  - [2+2] Photocyclizations.
  - Electrocyclic ring closures.
  - Ene-photooxygenations.
  - TiO_2 photocatalysis.

Vapourtec Ltd (*https://www.vapourtec.com*).

Photodecarboxylative cyclization



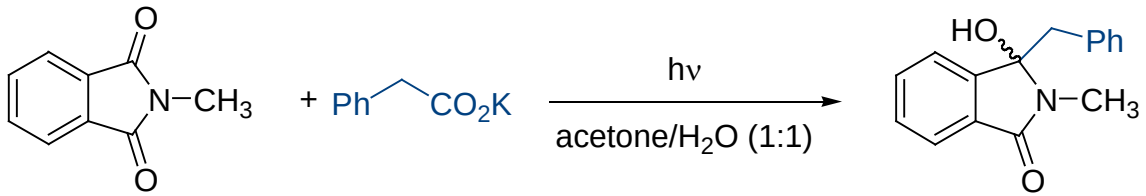
- Conditions:
  - 8-16 mM Pht=Gaba-OK in acetone/H_2O (1:1).
  - 82 W (>290 nm); 32°C; 4 bar (BPR).
  - Flow rate: 10 ml/min; residence time: 1 min.

c (mM)	Yield (%)	c (mM)	Yield (%)	c (mM)	Yield (%)
8	>95	11	86	15	83
10	**87**	13	84	16	75

- Scale-up:
  - 2000 ml of 10 mM Pht=Gaba-OK in acetone/H_2O (1:1).
  - 2.89 g (76%) after 200 min or 21 g/day.

M. Oelgemöller et al. *Chem. Eng. Technol.* **2016**, *39*, 81.

Photodecarboxylative benzylation



- Conditions:
  - 10-20 mM Pht=N-CH_3 with 3 eq. $PhCH_2CO_2K$ in acetone/H_2O.
  - 82 W (>290 nm); 32°C; 4 bar (BPR).
  - Flow rate: 10 ml/min; residence time: 1 min.

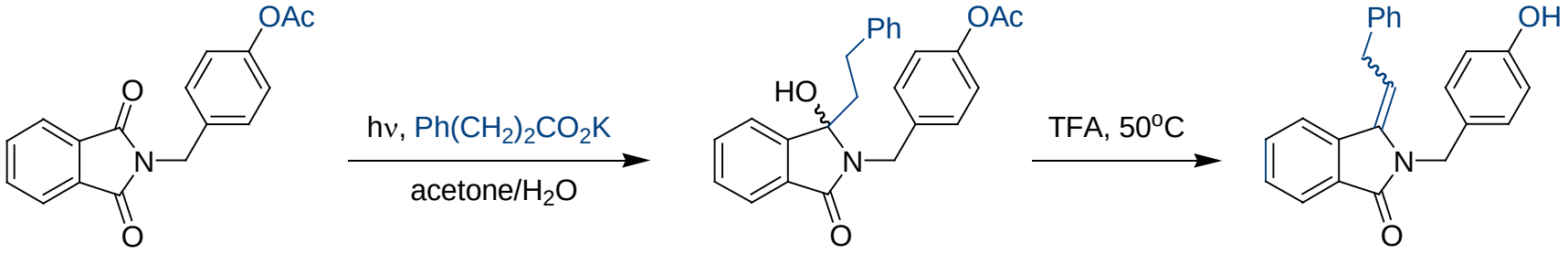
c (mM)	Conv. (%)	c (mM)	Conv. (%)	c (mM)	Conv. (%)
10	**100**	12	84	15	60
11	92	14	66	20	46

- Scale-up:
  - 2000 ml of 10 mM Pht=N-CH_3 in acetone/H_2O (1:1).
  - 4.43 g (88%) after 200 min or 32 g/day.

M. Oelgemöller et al. *Chem. Eng. Technol.* **2016**, *39*, 81. Vapourtec *Application Note 56* (*https://www.vapourtec.com*).

Tandem Flow Chemistry

Photodecarboxylation **Dehydration/Deprotection**



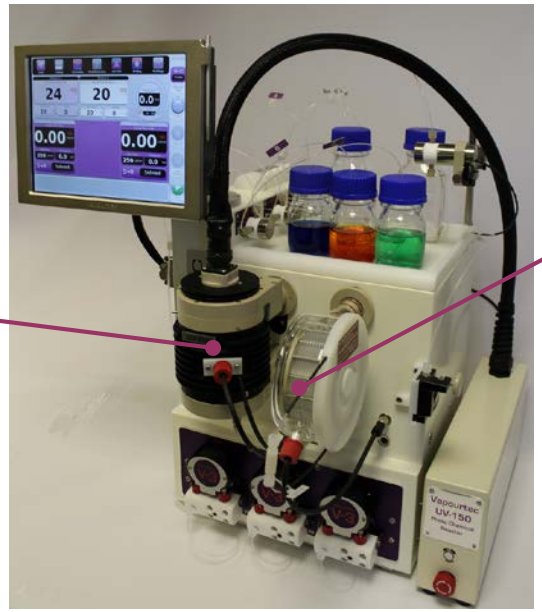
- Challenge: incomplete dehydration/deprotection.
- Approach: reduction of flow rate and neat TFA.

Cardiovascular

Y. Kato et al. *Chem. Pharm. Bull.* **1999**, *44*, 529.

Photo-module:

- FEP
- 1.3 mm (ID)
- 10 ml
- 82 W
- >290 nm filter
- 30-32°C

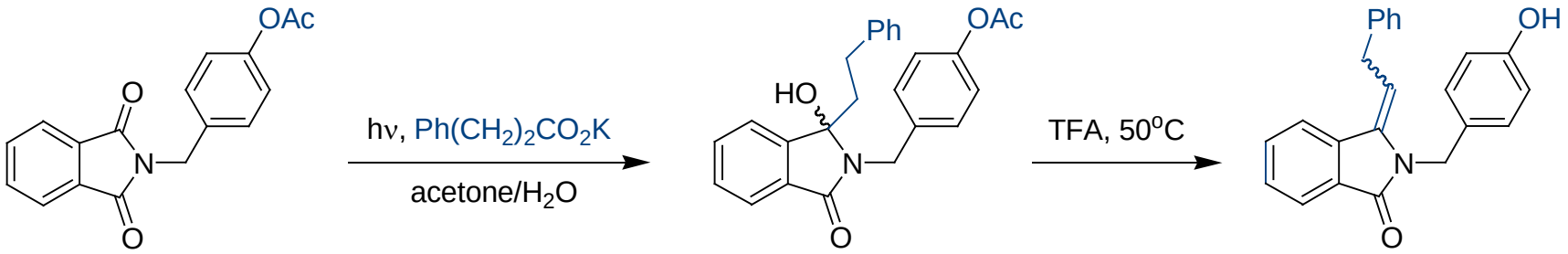


Thermo-module:

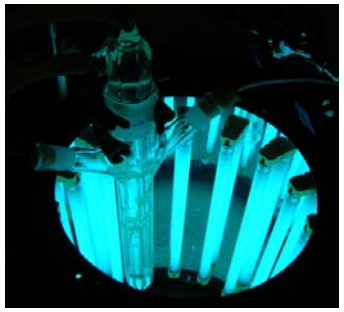
- PFA
- 10 ml
- 50°C

M. Oelgemöller et al. *Chem. Eng. Technol.* **2016**, *39*, 81.

Tandem Flow Chemistry



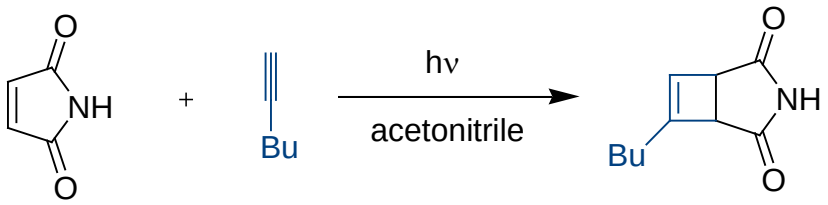
c (mM)	Flow rate (ml/min)	Photoreaction		Hydrolyses		Yield (%)
		r.t. (min)	Conversion (%)	r.t. (min)	Conversion (%)	
10	1.25	8	100	8	ca. 50%	—
0.5	**0.1**	**100**	**100**	**50**	**100**	**80**



Mode	Time	Yield (%)
batch	17 h	38
flow	**150 min**	**80**

M. Oelgemöller et al. *Chem. Eng. Technol.* **2016**, *39*, 81.

[2+2] Photocycloaddition



- Conditions:
  - 100 and 400 mM maleimide with 1.5 eq. 1-hexyne in acetonitrile.
  - 120 W (>220 nm); 30ºC; 4 bar (BPR).
  - Flow rates: 1-8 ml/min; residence times: 10-1¼ min.

c (mM)	r.t. (min)	Conv. (%)	c (mM)	r.t. (min)	Conv. (%)
100	**2½**	**95**	400	5	58
100	1¼	53	400	2½	29
400	**10**	**92**	400	1¼	15

- Scale-up:
  - 120 ml of 100 mM maleimide in acetonitrile.
  - 1.66 g (77%) after 30 min or 80 g/day.

Vapourtec *Application Note 36* (*https://www.vapourtec.com*).

[2+2] Photocycloaddition

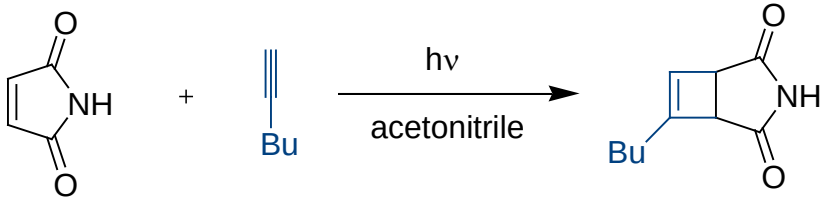
- Additional reaction parameters:
  - Wavelengths and temperature effects.
- Conditions:
  - 100 mM maleimide with 1.5 eq. 1-hexyne in acetonitrile.
  - 120 W (>220 nm or >290 nm); 30 or 60°C; 4 bar (BPR).
  - Flow rate: 4 ml/min; residence time: 2½ min.

c (mM)	r.t. (min)	λ (nm)	T (°C)	Conv. (%)
100	**2½**	**>220**	**30**	**95**
100	2½	>220	60	86
100	2½	>290	60	24

- Conclusion: easy and rapid optimization and scale-up.

Vapourtec *Application Note 36* (*https://www.vapourtec.com*).

[2+2] Photocycloaddition

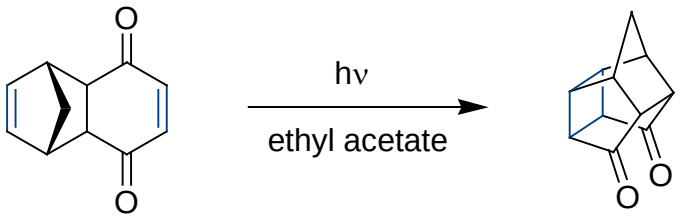


- Conditions:
  - 20 mM maleimide with 1.5 eq. 1-hexyne in acetonitrile.
  - 9 W low pressure Hg-lamp (254, 310 or 370 nm); 30°C.
  - Flow rates: 1-4 ml/min; residence times: 10-2½ min.

c (mM)	r.t. (min)	λ (nm)	Conv. (%)	Produc. (g/d)
20	5	370	11	1.2
20	5	310	84	8.7
20	5	254	95	9.8
20	10	310	96	4.9
20	**2½**	**254**	**71**	**14.6**

Vapourtec *Application Note 47* (*https://www.vapourtec.com*).

[2+2] Photocyclization



- Conditions:
  - 200 mM dihydronaphthoquinone in ethyl acetate.
  - 60 W LED (365 nm); 0-60ºC.
  - Flow rates: 2.5 or 6.7 ml/min; residence times: 4 or 1½ min.

c (mM)	r.t. (min)	T (ºC)	Conv. (%)	Produc. (g/d)
200	4	30	100	168
200	**1½**	**30**	**96**	**319**
200	1½	0	95	317
200	**1½**	**15**	**96**	**322**
200	1½	60	94	314

Vapourtec *Application Note 44* (*https://www.vapourtec.com*).

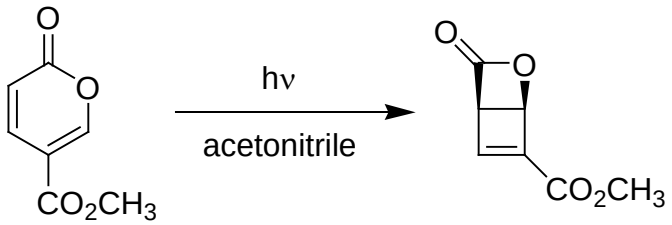
[2+2] Photocyclization

- Additional reaction parameters:
  - Concentration and residence time to completion.
- Conditions:
  - 100-800 mM dihydronaphthoquinone in ethyl acetate.
  - 60 W LED (365 nm); 30ºC.
  - Flow rates: 1.7-13.3 ml/min; residence times: 6-¾ min.

c (mM)	r.t. (min)	T (ºC)	Conv. (%)	Produc. (g/d)
100	¾	30	90	302
200	1½	30	96	320
400	3	30	99	331
800	**6**	**30**	**99.5**	**334**

Vapourtec *Application Note 44* (*https://www.vapourtec.com*).

Electrocyclic ring closure



- Conditions:
  - 100 mM methyl coumalate in acetonitrile.
  - 75 W (>220 nm and >290 nm); 15°C; 4 bar (BPR).
  - Flow rates: 0.08 or 0.17 ml/min; residence times: 120 or 60 min.

c (mM)	r.t. (min)	λ (nm)	Conv. (%)	Impur. (%)
100	60	>220	~20	~13
100	60	>290	~20	~2
100	120	>220	~50	~20
100	**120**	**>290**	**~50**	**~5**

Vapourtec *Application Note 37* (*https://www.vapourtec.com*).

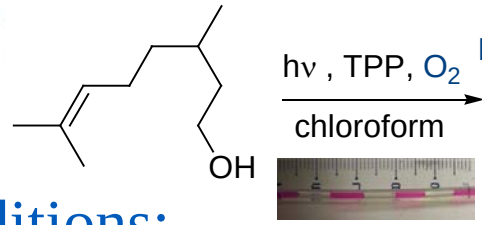
Electrocyclic ring closure

- Additional reaction parameters:
  - Concentration, lamp power and temperature effects.
- Conditions:
  - 50 or 100 mM methyl coumalate in acetonitrile.
  - 75 W or 120 W (>290 nm); 0-30°C; 4 bar (BPR).
  - Flow rate: 0.17 ml/min; residence time: 60 min.

c (mM)	T (°C)	Lamp (W)	Conv. (%)	Impur. (%)
100	0	75	~30	~2
50	0	75	~60	~7.5
50	**0**	**120**	**~88**	**~7.5**
50	15	120	~83	~14
50	30	120	~78	~19

Vapourtec *Application Note 37* (*https://www.vapourtec.com*).

Ene-photooxygenations



- Conditions:
  - 200 mM citronellol and 2 mM TPP in chloroform.
  - 18 W (output) LED (420 nm); 30°C; 8 bar (BPR).
  - Flow rates: 8.53 ml/min (reagents) and 3.2-10 ml/min (O_2).

Reagents (ml/min)	O_2 (ml/min)	Molar ratio	Approx. r.t. (s)	Conv. (%)	Produc. (g/d)
8.53	5.12	1 : 1	71	74	286
8.53	3.2	1 : 0.5	75	46	175
8.53	**6.4**	**1 : 1.25**	**69**	**89**	**341**
8.53	10	1 : 2	52	88	336

Vapourtec *Application Note 43* (*https://www.vapourtec.com*).

Ene-photooxygenations

- Additional reaction parameters:
  - Concentrations, flow rate and exposure time effects.
- Conditions:
  - 200 or 400 mM citronellol and 2 or 4 mM TPP in chloroform.
  - 18 W (output) LED (420 nm); 30ºC; 8 bar (BPR).
  - Flow rates: 1.6-8.53 ml/min for reagents and O_2 (1.25 eq.).

citronellol (mM)	Reagents (ml/min)	O_2 (ml/min)	Approx. r.t. (s)	Conv. (%)	Produc. (g/d)
200	2.14	1.6	281	95	91
200	4.27	3.2	135	95	182
200	6.37	4.8	99	92	264
200	**8.53**	**6.4**	**67**	**89**	**341**
400	4.27	6.4	118	88	338

Vapourtec *Application Note 43* (*https://www.vapourtec.com*).

Ene-photooxygenations

- Additional reaction parameters:
  - TPP concentration effect.
- Conditions:
  - 200 mM citronellol and 4-0.00008 mM TPP in chloroform.
  - 18 W (output) LED (420 nm); 30ºC; 8 bar (BPR).
  - Flow rates: 8.53 ml/min (reagents) and 6.4 ml/min (O_2; 1.25 eq.).

TPP (µM)	Molar ratio	Conversion (%)	Produc. (g/d)
4000	1 : 50	82	314
500	1 : 400	94	360
125	**1 : 1600**	**96**	**367**
8	1 : 25000	90	346
0.8	1 : 250000	48	185

Vapourtec *Application Note 43* (*https://www.vapourtec.com*).

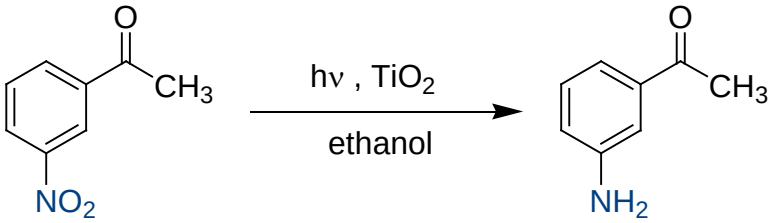
Ene-photooxygenations

- Additional reaction parameters:
  - Productivity.
- Conditions:
  - 200 mM citronellol and 0.125 mM TPP (1:1600) in chloroform.
  - 18 W (output) LED (420 nm); 30ºC; 8 bar (BPR).
  - Flow rates: 8.53 or 10 ml/min (reagents) and 6.4 or 7.5 ml/min (O_2; 1.25 eq.).

citronellol (mM)	Reagents (ml/min)	O_2 (ml/min)	Conv. (%)	Produc. (g/d)
200	**8.53**	**6.4**	**96**	**367**
200	10	7.5	81	362

Vapourtec *Application Note 43* (*https://www.vapourtec.com*).

TiO_2 photocatalysis



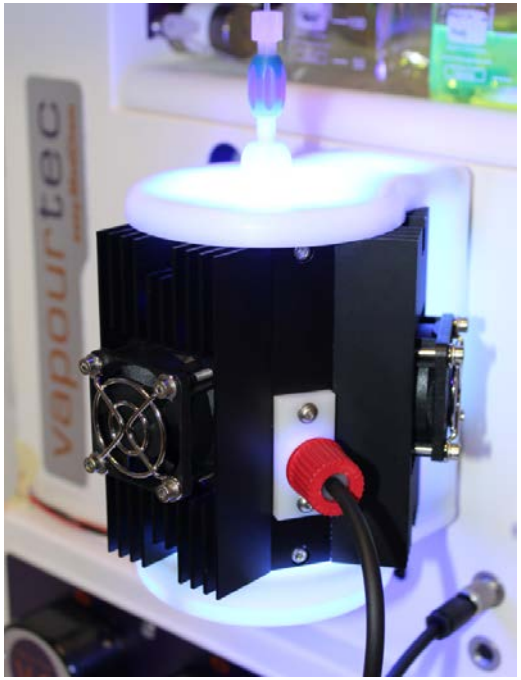
- Conditions:
  - 10 mM 3-nitroacetophenone with 10 mg/ml TiO_2 P25 in ethanol.
  - 60 W LED (365 nm); 70°C; 3 bar (BPR).
  - Flow rates: 6.7-15 ml/min; residence times: 1½-⅔ min.

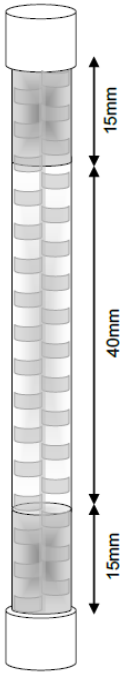
c (mM)	TiO_2 (mg/ml)	r.t. (min)	Conversion (%)
10	10	1.5	99
10	10	1.0	99
10	**10**	¾	**99**
10	10	⅔	87
10	0	10	no reaction

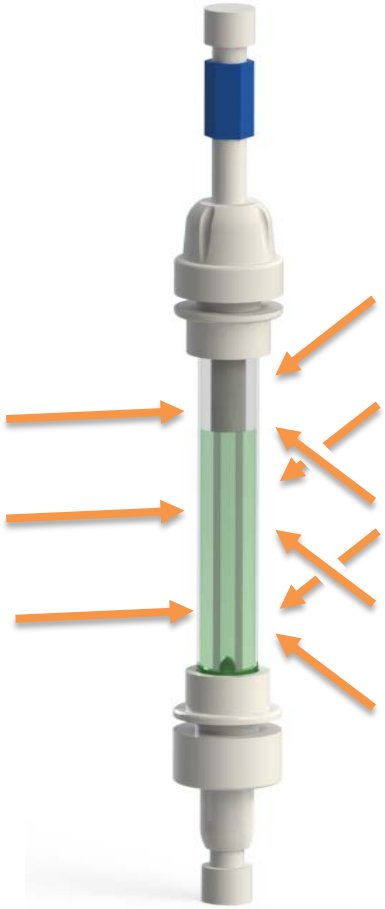
Vapourtec *Application Notes 41 and 42* (*https://www.vapourtec.com*).

Packed bed column

- Features:
  - Solid-supported photocatalysts (e.g. TiO_2 on hollow glass beads).
  - LED illumination applied around column.
  - Temperature control from -20°C to 80°C.
  - Wavelength ranges 365 nm to 700 nm.







Vapourtec *Application Note 46* (*https://www.vapourtec.com*).

Conclusion

- The Vapourtec UV-150 Reactor:
  - Allows for easy transfer of a variety of photoreactions from 'batch to flow'.
  - Enables rapid and safe photochemical process optimization.
  - Allows for convenient scale-up and *in series* coupling with thermal processes.
  - Is at present the most versatile and advanced continuous flow photoreactor on the market with potential as '*gold standard*'.
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