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Title:	Chiroptical Signatures & Photocatalytic Destruction of Organophosphorus Nerve Agents
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"Chiroptical Signatures & Photocatalytic Destruction of Organophosphorus Nerve Agents"

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April 24, 2019
DTRA Tech Watch
DTRA Headquarters, Fort Belvoir, VA

"It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change" – C. Darwin

"Chiroptical Signatures and Photocatalytic Destruction of Organophosphorus Nerve Agents"
An Outline

- "Where did we come from? Where are we going?"
- What is Chiroptical Induction? (= Tunable Asymmetric Photochemical Induction)
- CD & Anisotropy Spectra of Amino Acids
- Chiroptical Induction in Thin Amorphous Solid Films
- CD & Anisotropy Spectra of Small Molecule Building Blocks – Experimental & Theoretical
- Chiroptical Induction/Photolysis in Solution – Batch (vs. Flow)
- Flow Chemistry – An Introduction
- Chiroptical Photocatalytic Destruction of Organophosphorus Analogs
- Future Trajectories

"Where did we come from? Where are we going?"

χειρ "hand"

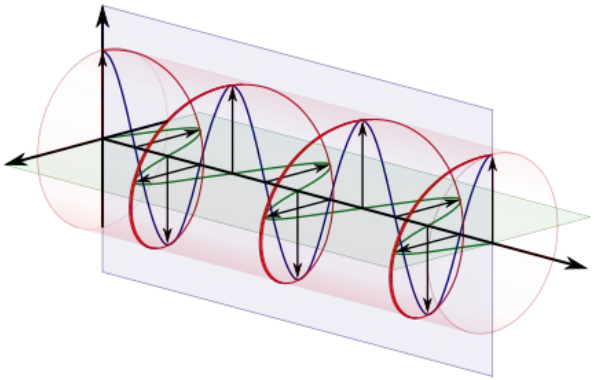
"There can be now no doubt of the connection of the crystalline forces with magnetism and electricity. It seems to me now all but certain that the space or ether (?) surrounding an electrified wire or a magnet is in the same state with the space or ether intervening between the molecules of plagiedral crystals. Polarized light is the test of that state—a helicoidal, dissymmetrical state."
- J.F.W. Herschel, in a letter to Faraday in 1845

'les deux extrémités du prisme sont dissymétriques" ("the two extremities of the prism are dissymmetric")
– L. Pasteur, *Memoir on the relationship that may exist between crystalline form and chemical composition, and on the cause of optical rotation,*1848

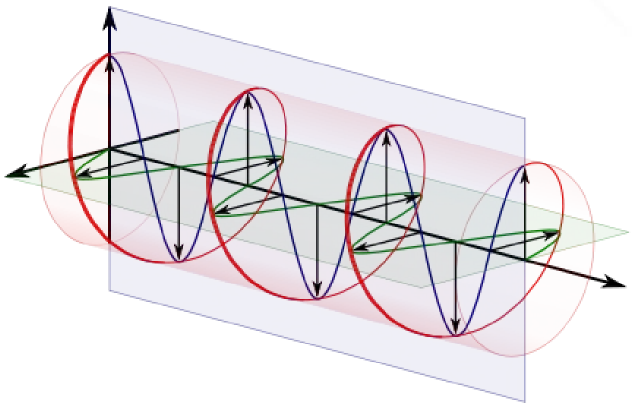
"I call any geometrical figure, or group of points, chiral, and say that it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."
– Lord Kelvin, *Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light*, 1884

Chiroptical Induction:
The use of circularly polarized light (cpl) to induce chirality

What is cpl?



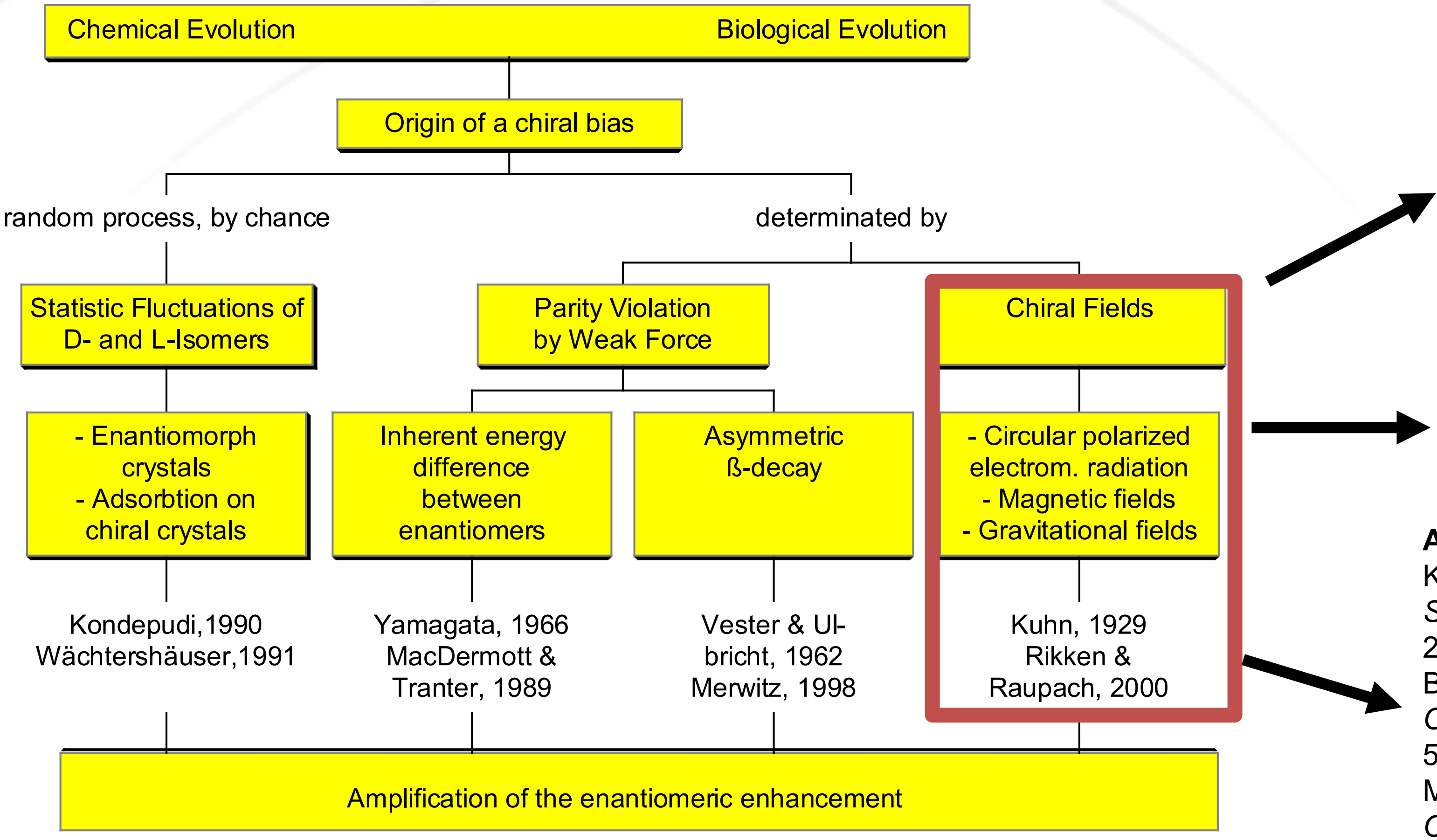
Left-handed cpl (l-cpl)



Right-handed cpl (r-cpl)

The Rose Chafer beetle (Cetonia aurata), whose external surface reflects only l-cpl.

Chiroptical "Induction":
The Origin of Chirality….Asymmetric Light Fields?



Asymmetric Synthesis
Kagan, et. al., *J. Mol. Evol.*, 1974, *4*, 41–48.

Asymmetric Isomerization
Rijeesh,et. al. *Chem.Sci.*, 2015, *6*, 973–980.
Stevenson, et. al. *Mol. Photochem.*, 1969, *1*,271–288.

Asymmetric Photolysis
Kagan, et. al. *Top. Stereochem.*, 1988, *18*, 249–330.
Balavoine, et. al. *J. Am. Chem. Soc.*, 1974, *96*, 5152–5158.
Meinert, et. al. *Angew. Chem., Int. Ed.*, 2014, *53*, 210–214.

Meierhenrich et al.: Photochemical Origin of Biomolecular Asymmetry. In: Ehrenfreund P., Angerer O., Battrick B. (Eds.) *Exo-/Astro-Biology*, European Space Agency, ESA SP-496, ISBN 92-9092-806-9, Noordwijk, The Netherlands (2001), p. 167-170.

Chiroptical Signatures:
CD & Anisotropy Spectra

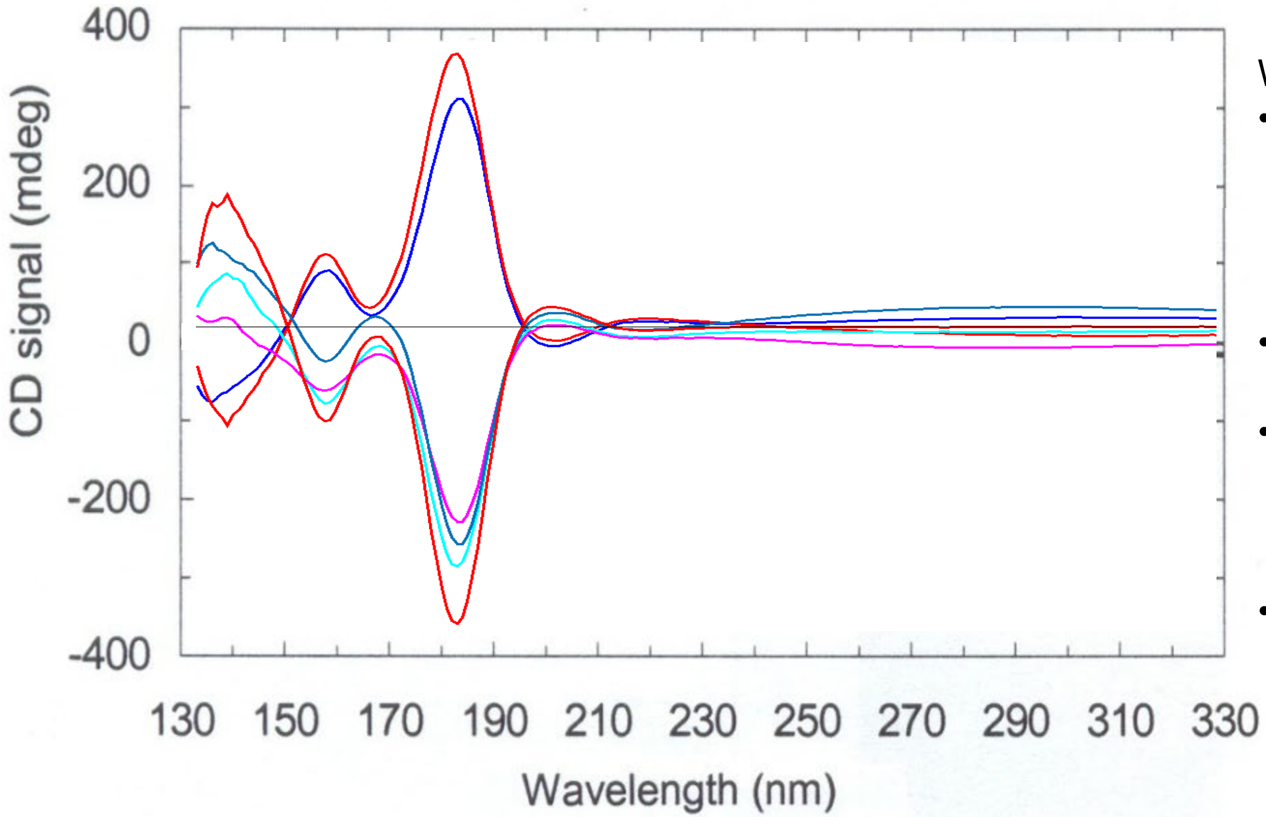
What is a "**CD**" Spectrum?
CD = Circular Dichroism
Differential absorption of l-cpl and r-cpl, used to determine secondary structure of biomolecules and optical isomerism of molecules.

$$\Delta\varepsilon = \varepsilon_L - \varepsilon_R$$

What is an "**Anisotropy**" Spectrum?
Anisotropy (*g*) is the extent to which a chiral molecule is affected by cpl. (CD signal divided by absorption signal)

$$g = \Delta\varepsilon/\varepsilon$$

Chiroptical Signatures:
CD & Anisotropy Spectra of Amino Acids



What is a "Cotton Effect"?

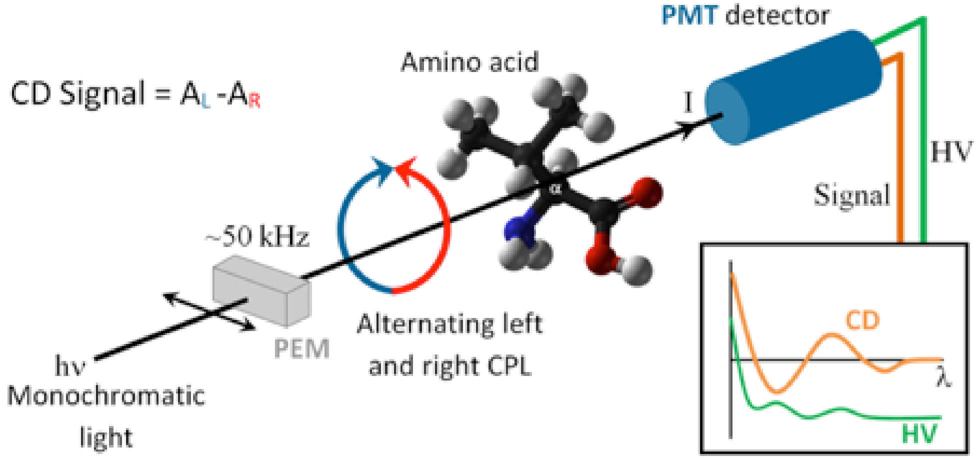
- Characteristic changes in optical rotary dispersion and/or circular dichroism in the vicinity of an absorption band
- Discovered in 1895 by Cotton.
- Positive if optical rotation increases as wavelength decreases, negative if rotation first decreases.
- Beta sheet protein structures show negative Cotton effects.

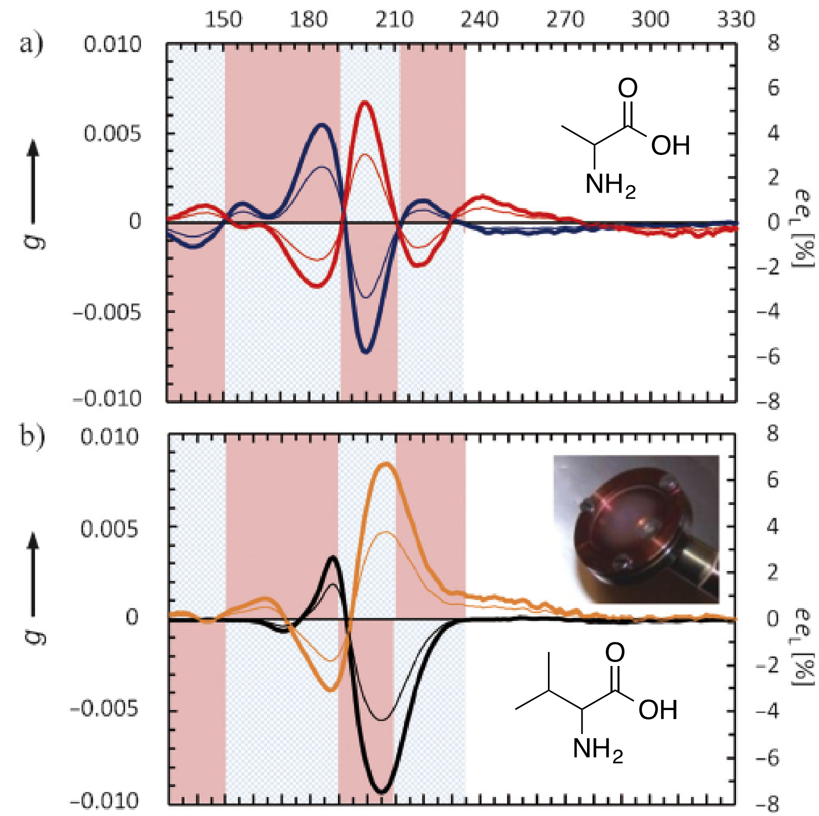
Vacuum ultra violet circular dichroism spectrum of amorphous solid-state alanine enantiomers. Blue and red lines: L-alanine. Rose, green, turkish and bright red lines: D-alanine.

Meierhenrich et al.: *Angew. Chem. Int. Ed.,* **49** (2010), 7799-7802.

Chiroptical Signatures:

CD & Anisotropy Spectra of Amino Acids





Difference in Extinction Coefficients of Enantiomers (CD spectrum): $\Delta\varepsilon = \varepsilon_L - \varepsilon_R$

Anisotropy Factor: $g = \Delta\varepsilon/\varepsilon$

a) Anisotropy spectra of isotropic amorphous D-Ala (red) and L-Ala (blue); b) D-Val (orange) and L-Val (black).

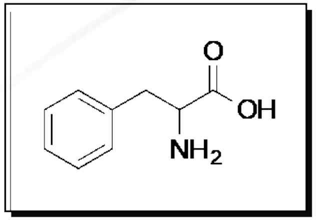
Predicting CPL-induced %ee's:

$$ee \geq (1-(1-\xi)^{g/2}) \times 100\%$$

Meinert et al.: *Angew. Chem. Int. Ed.* **51** (2012), 4484-4487

Chiroptical Signatures:

CD & Anisotropy Spectra of Amino Acids

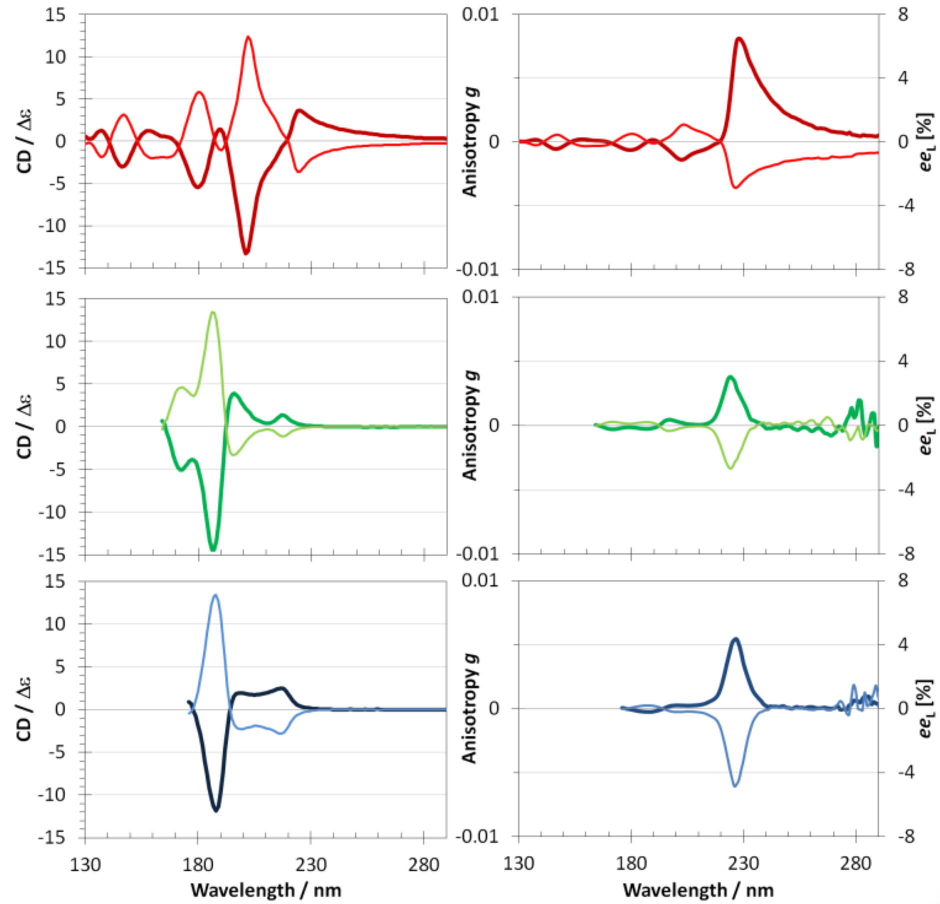


Amorphous Solid

Solvent = 1,1,1,3,3,3-hexafluoropropan-2-ol (HFiP)

$$ee \geq (1-(1-\xi)^{g/2}) \times 100\%$$

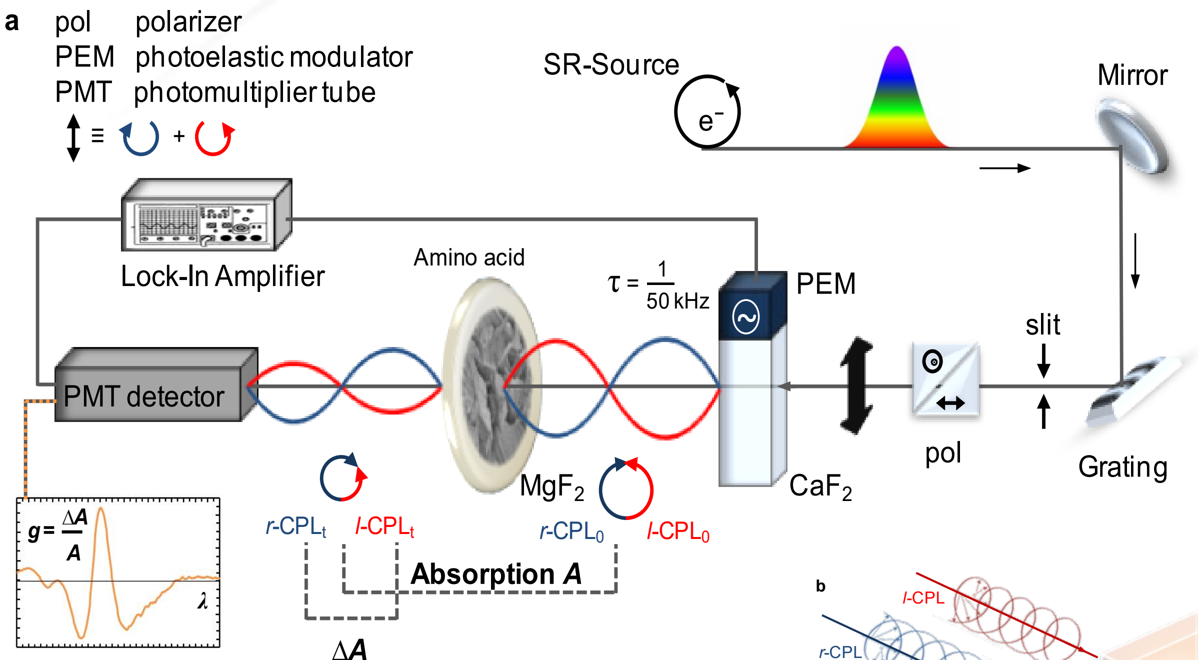
Solvent = Water

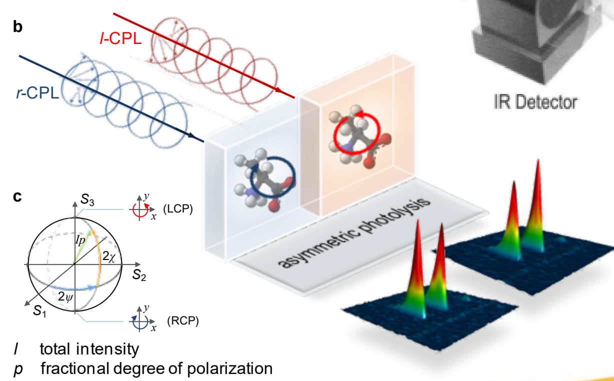


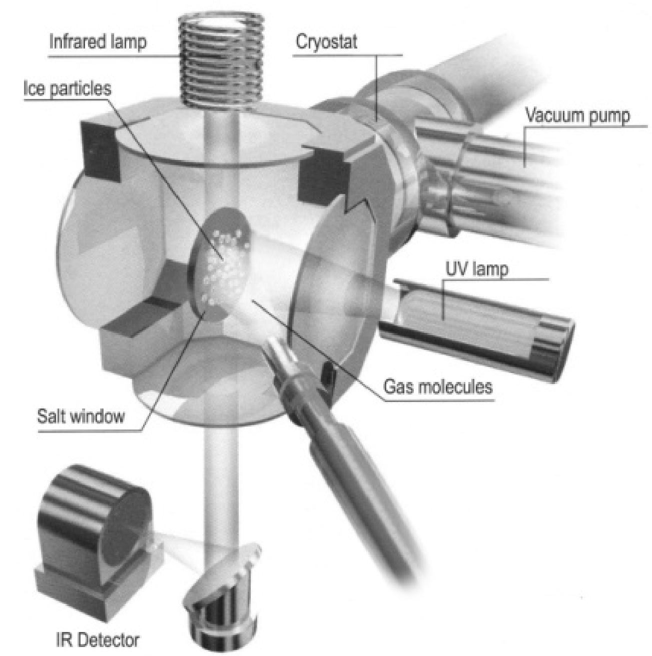
Bredehöft *et. al.: Chirality*, **26(8)** (2014) 373-378; **DOI:** 10.1002/chir22329
Evans et al: *Top. Curr. Chem.*, **341**, **(**2013), 271-299; **DOI:** 10.1007/128_2013_442

Chiroptical Induction:

CPL Asymmetric Photolysis of Alanine
Amorphous thin film (solid)



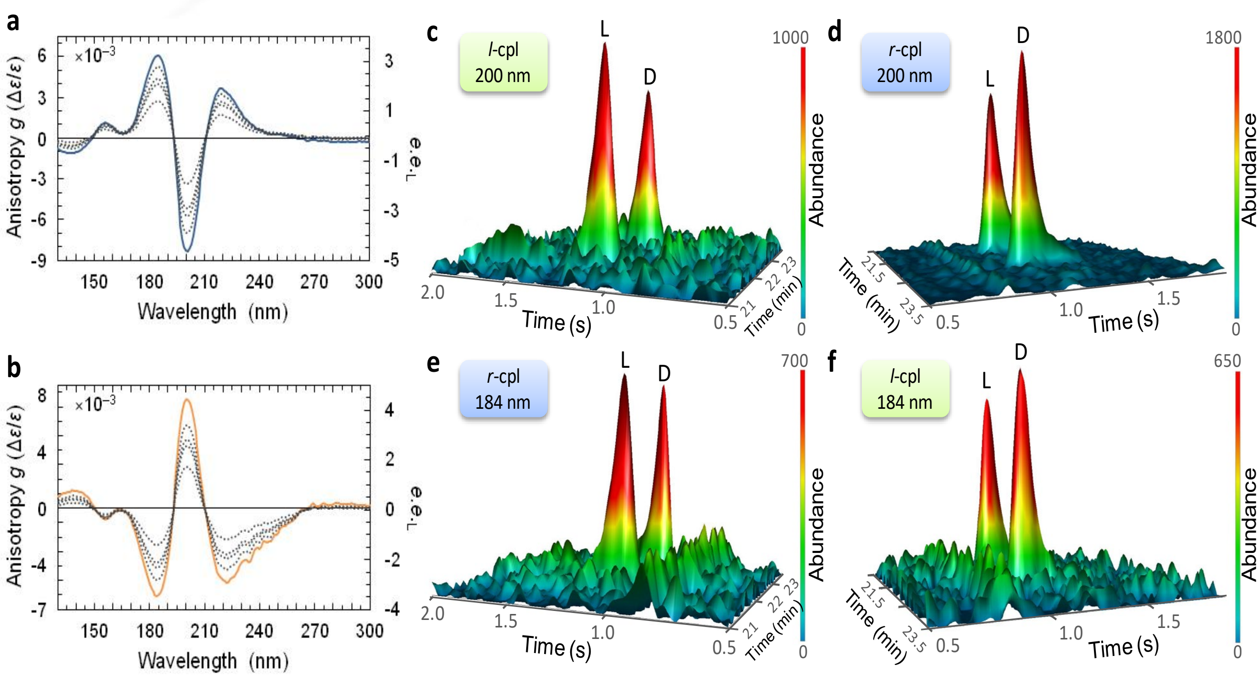




Meinert et al.: *Angew.Chem. Int. Ed.* **53(1)**, (2014), 210-214*;* **DOI:** 10.1002/anie.201307855

Chiroptical Induction:

CPL Asymmetric Photolysis of Alanine Amorphous thin film (solid)



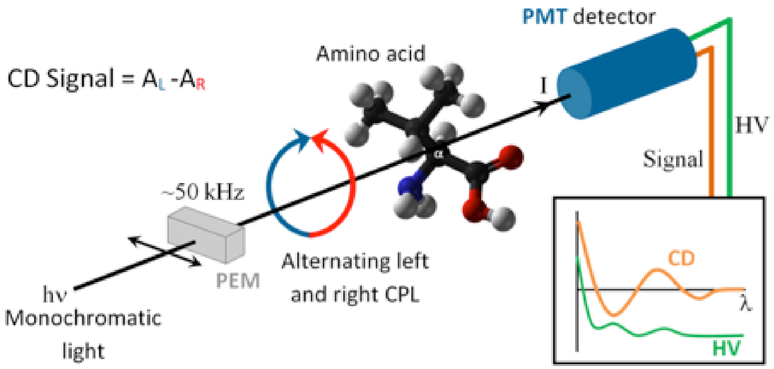
Irradiation Time (hours)	Irradiation Wavelength (nm/eV)	r-cpl/l-cpl	% e.e
5.0	200/6.19	l-cpl	3.1
5.0	200/6.19	r-cpl	-3.4
2.5	200/6.19	l-cpl	2.2
2.5	200/6.19	r-cpl	-2.4
5.0	184/6.74	l-cpl	-2.2
5.0	184/6.74	r-cpl	2.4
2.5	184/6.74	l-cpl	-2.1
2.5	184/6.74	r-cpl	1.9

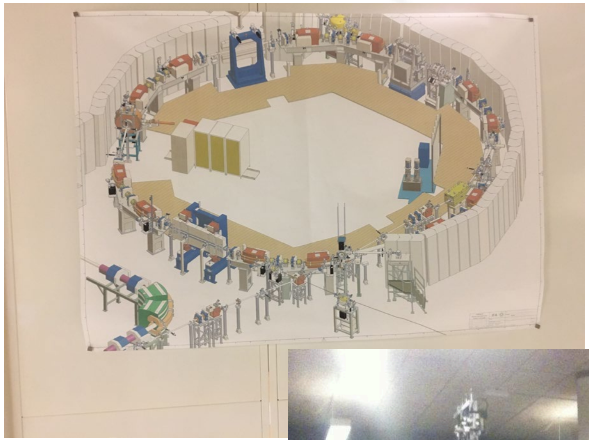
DESTRUCTIVE

Meinert et al.: *Angew.Chem. Int. Ed.* **53(1)**, (2014), 210-214*;* **DOI:** 10.1002/anie.201307855

Chiroptical Signatures – Synchrotron Radiation Circular Dichroism (SRCD): (Aarhus University, Denmark)

CD & Anisotropy Spectra of Small Molecule Building Blocks/APIs

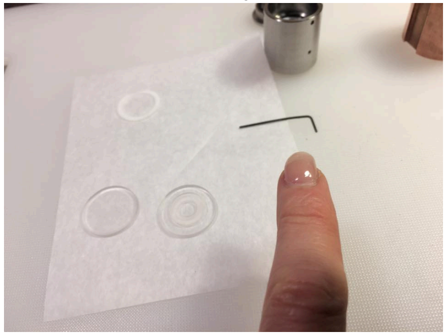




Cell & Holder for CD & anisotropy spectra

Cell & Holder for CD & anisotropy spectra

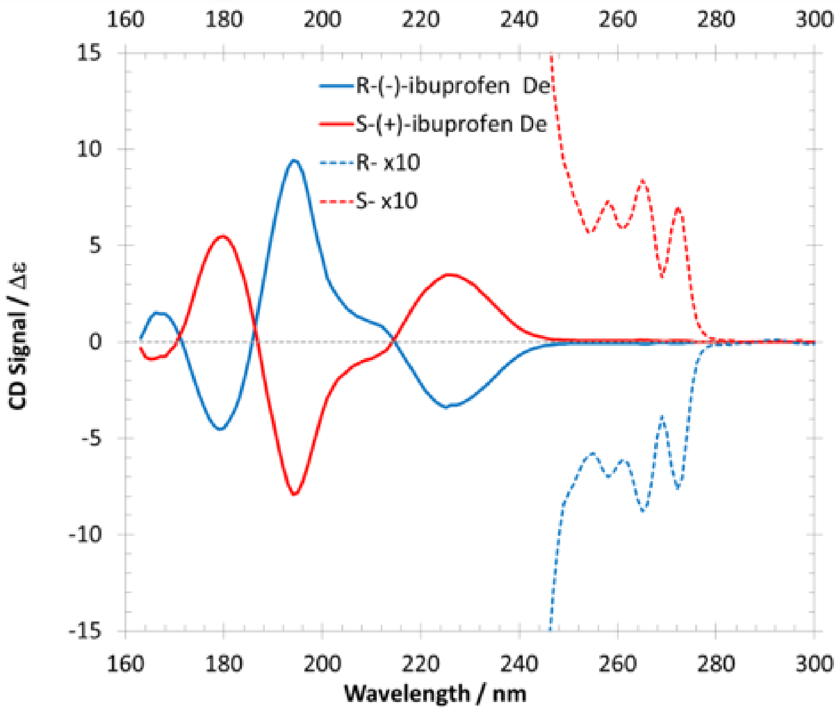
Cell & Holder for CD & anisotropy spectra

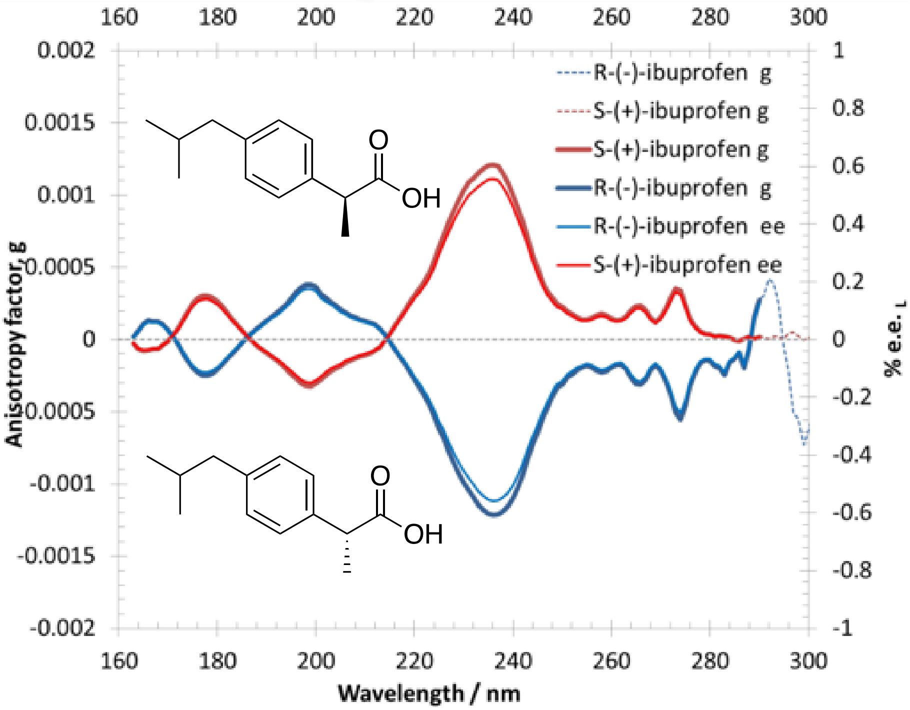


Evans et al.: *Chem. Commun.* In preparation.
Evans et al.: *Phys. Chem. Chem. Phys.* In preparation.

Chiroptical Signatures:
CD & Anisotropy Spectra of Ibuprofen

In hexafluoroisopropanol (HFiP):

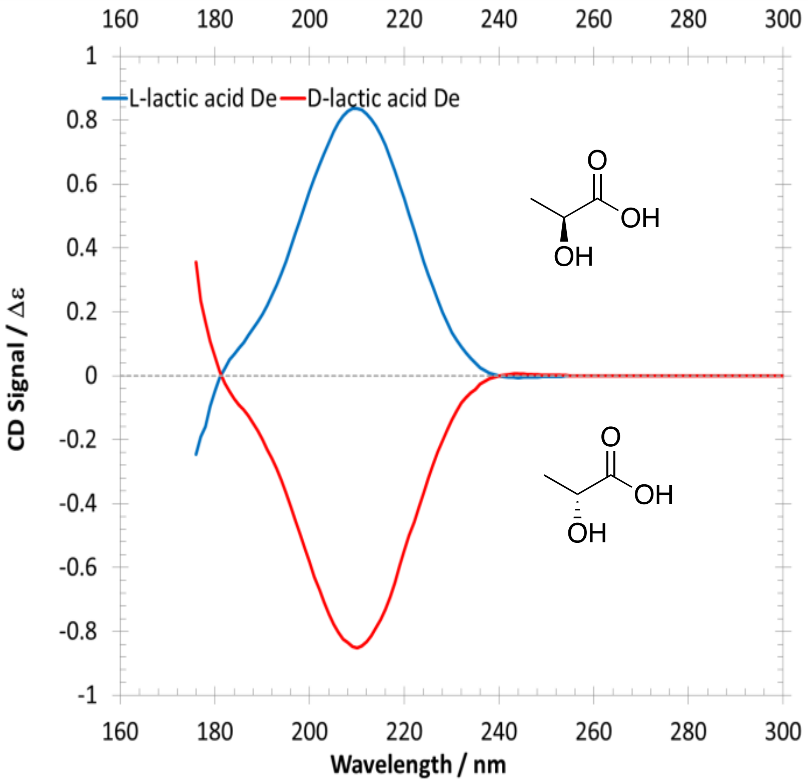


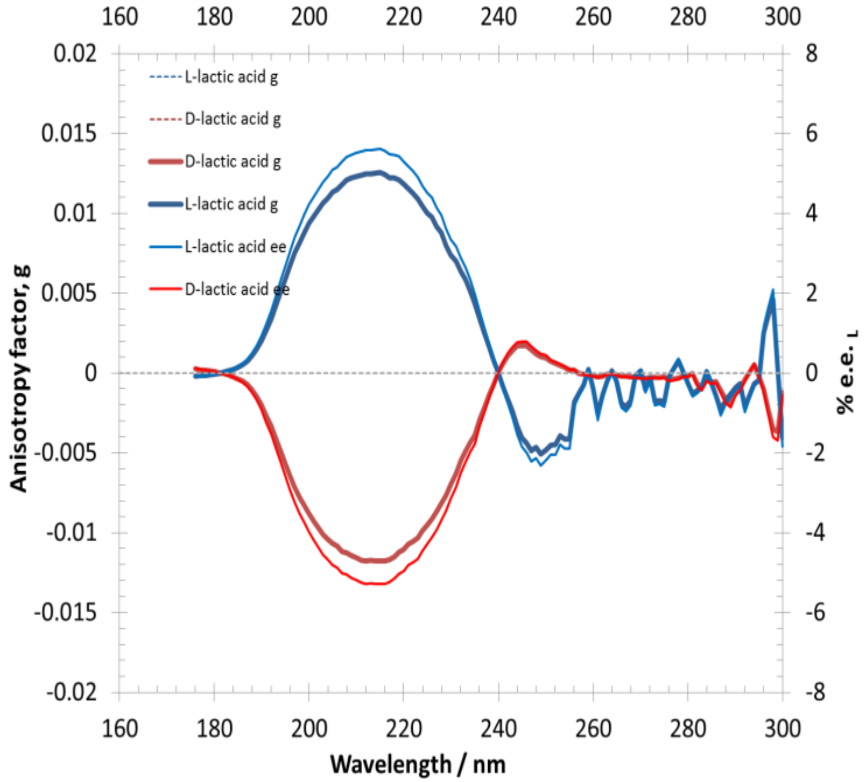


Evans et al.: *Chem. Commun.* In preparation.

Chiroptical Signatures:
CD & Anisotropy Spectra of Lactic Acid

In Water:

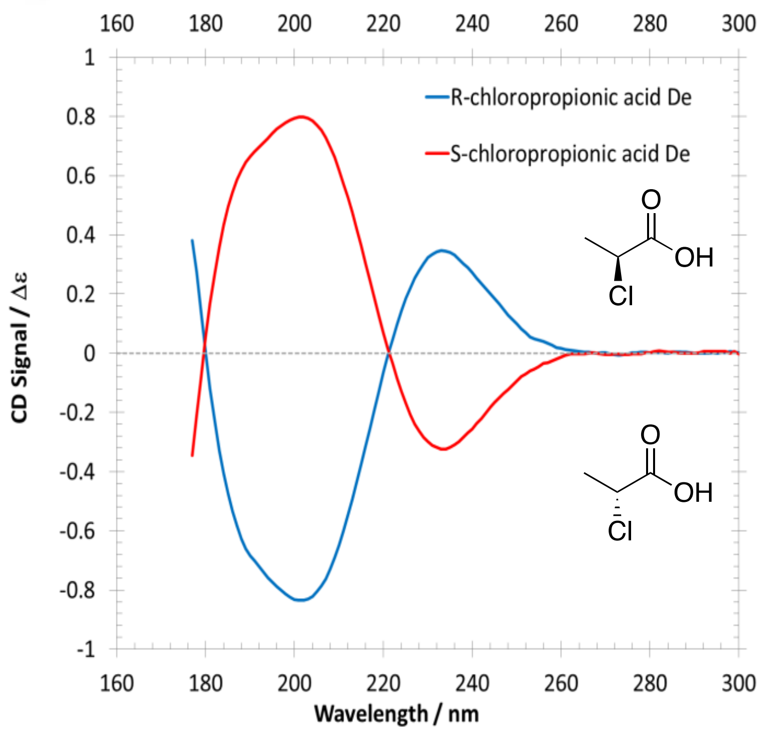


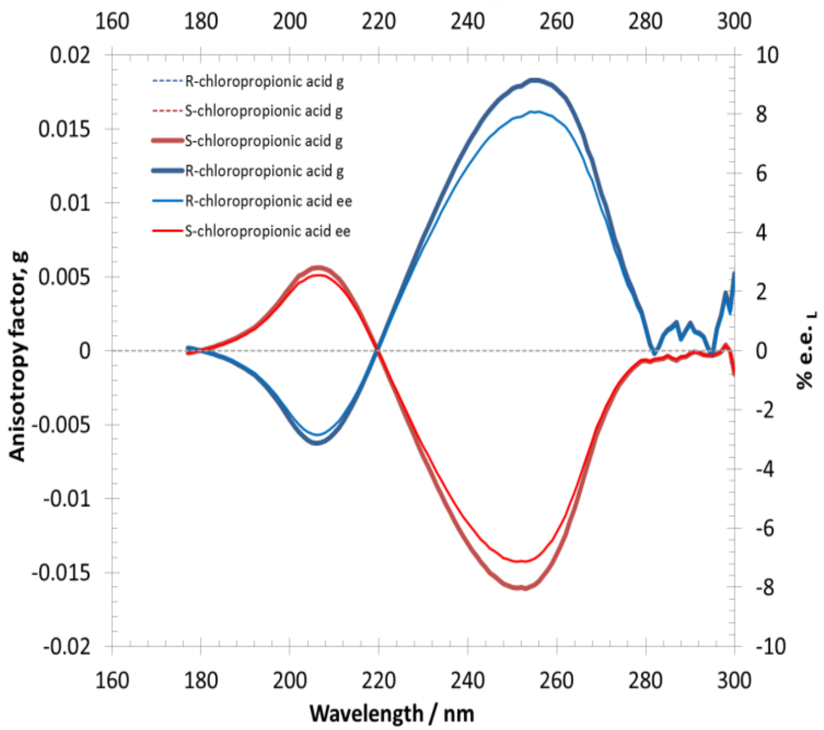


Evans et al.: *Chem. Commun.* In preparation.

Chiroptical Signatures:
CD & Anisotropy Spectra of 2-Chloropropionic Acid

In Water:

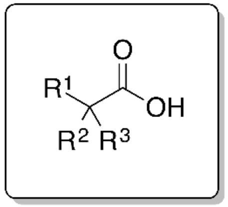


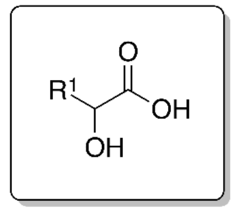


Evans et al.: *Chem. Commun.* In preparation.

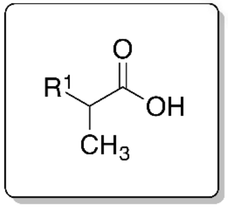
Chiroptical Signatures:

CD & Anisotropy Spectra of Small Molecule Building Blocks/APIs – The Current Experimental Library

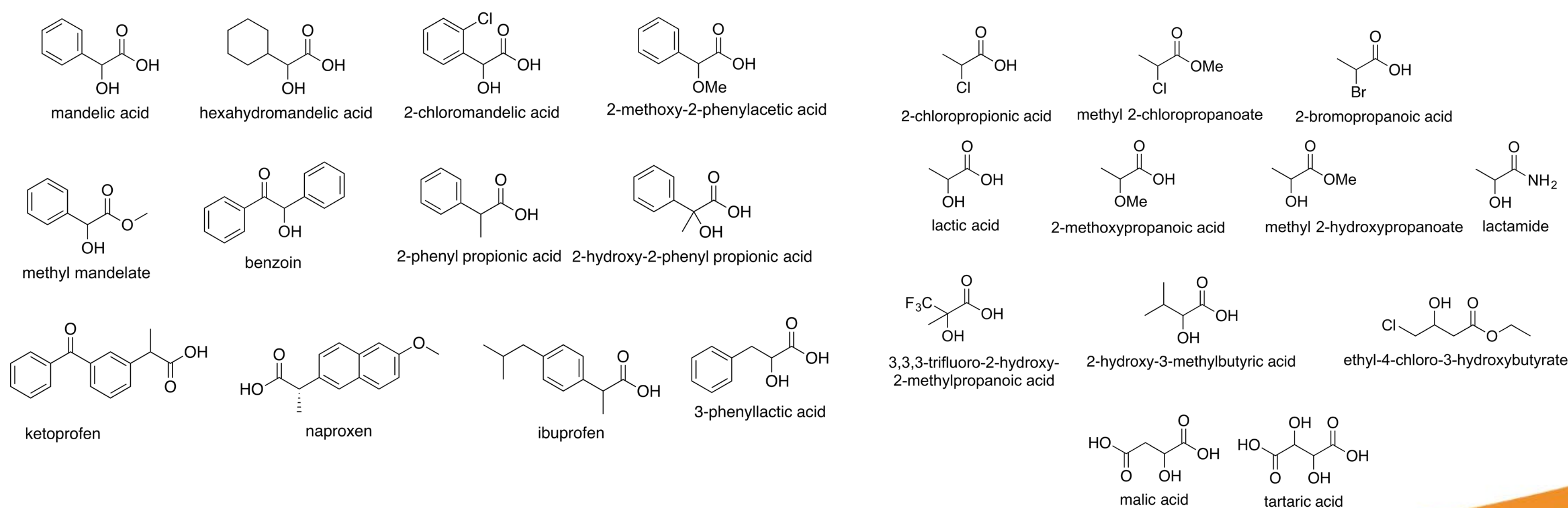




α-hydroxy acids



α-methyl acids/propionic acids

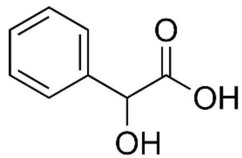


Evans et al.: *Chem. Commun.* In preparation.

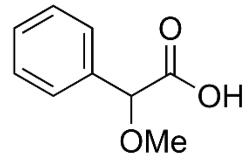
Chiroptical Singatures:

CD & Anisotropy Spectra of Small Molecule Building Blocks/APIs – TD-DFT Approaches

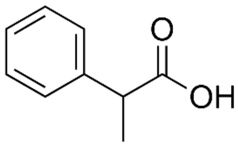
TD-DFT Modelling of CD spectra:
Collaboration with Dr. A. Petit & S. Guillen (CSU Fullerton, CA, USA)



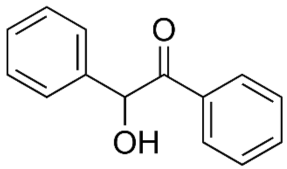
Mandelic acid



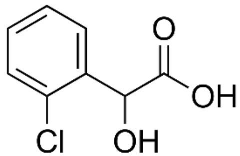
2-Methoxyphenylacetic acid



2-Phenylpropionic acid



Benzoin



2-Chloromandelic acid

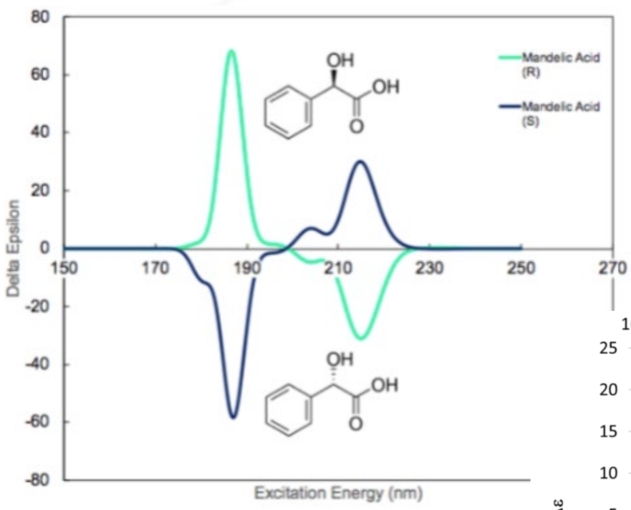
Currently collaborating with Dr. Amanda Neukirch for OP compounds (T-1, LANL)

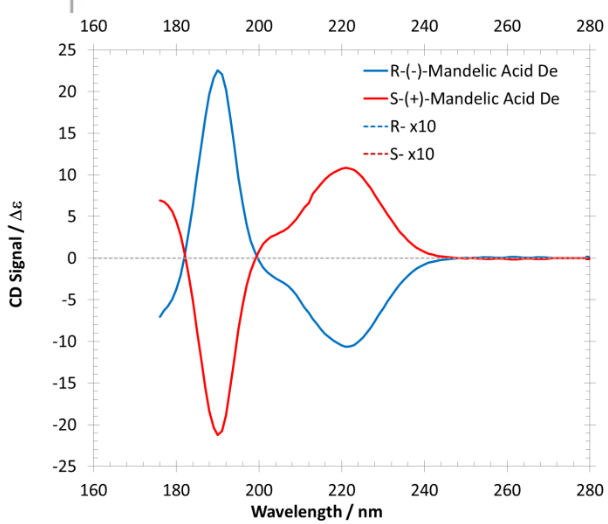
Evans et al.: *Phys. Chem. Chem. Phys.* In preparation.

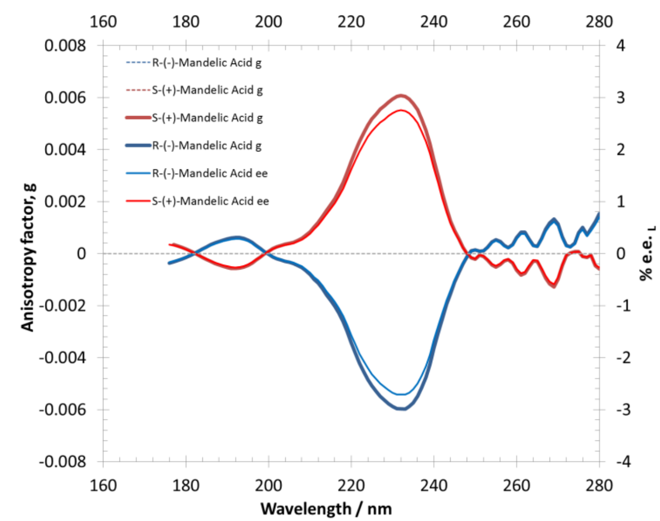
Chiroptical Singatures:

CD & Anisotropy Spectra of Small Molecule Building Blocks/APIs – TD-DFT Approaches

Mandelic Acid



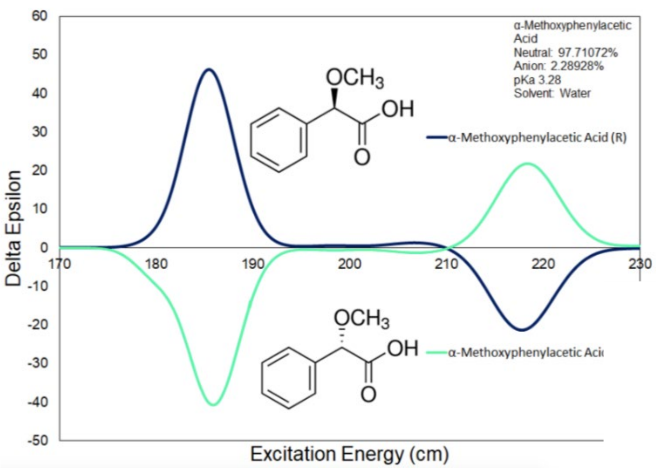




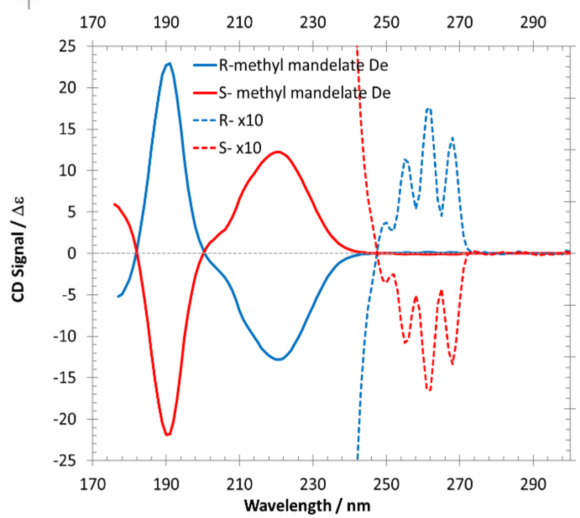
Evans et al.: *Phys. Chem. Chem. Phys.* In preparation.

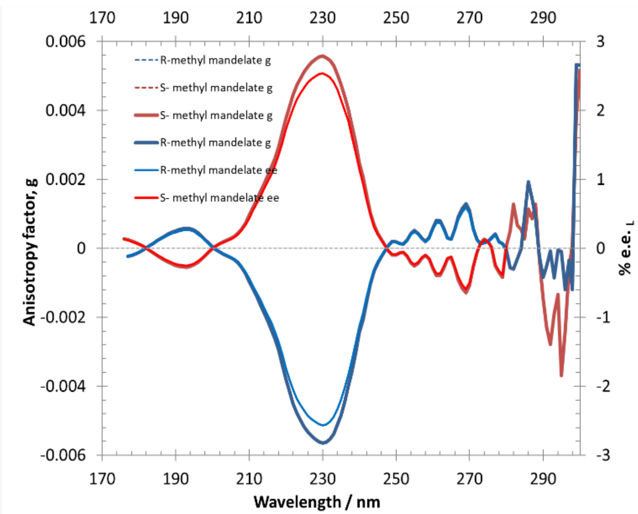
Chiroptical Singatures:

CD & Anisotropy Spectra of Small Molecule Building Blocks/APIs – TD-DFT Approaches



α-Methoxyphenylacetic acid





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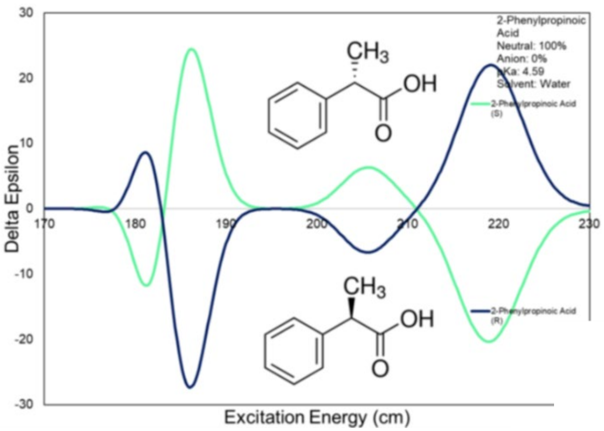
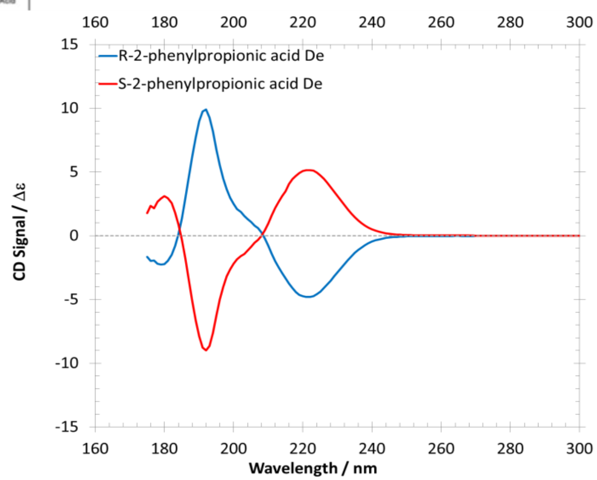
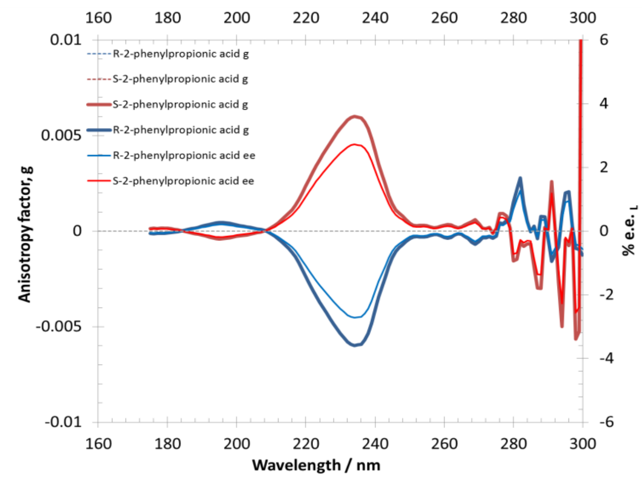
CD & Anisotropy Spectra of Small Molecule Building Blocks/APIs – TD-DFT Approaches



2-Phenylpropionic acid

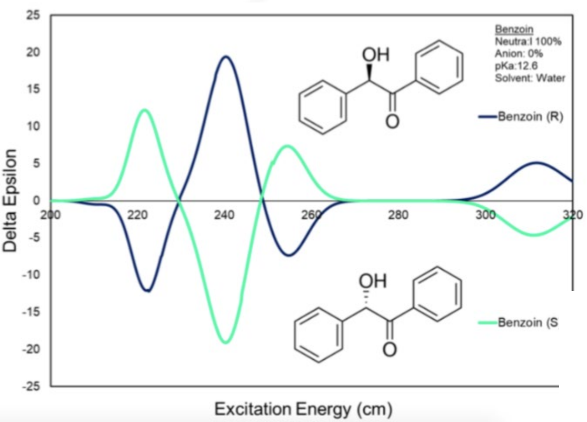




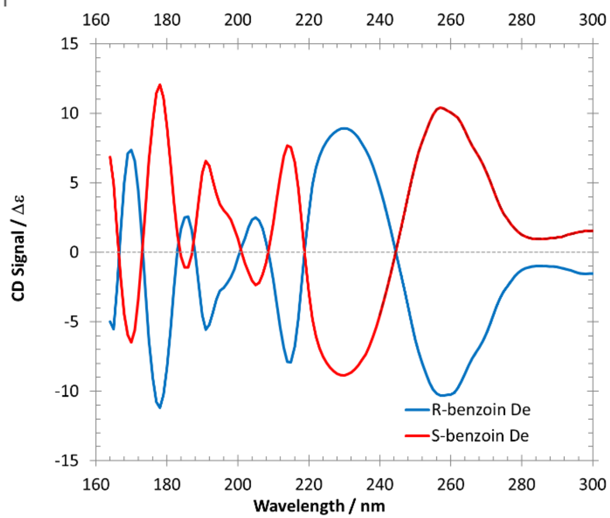
Evans et al.: *Phys. Chem. Chem. Phys.* In preparation.

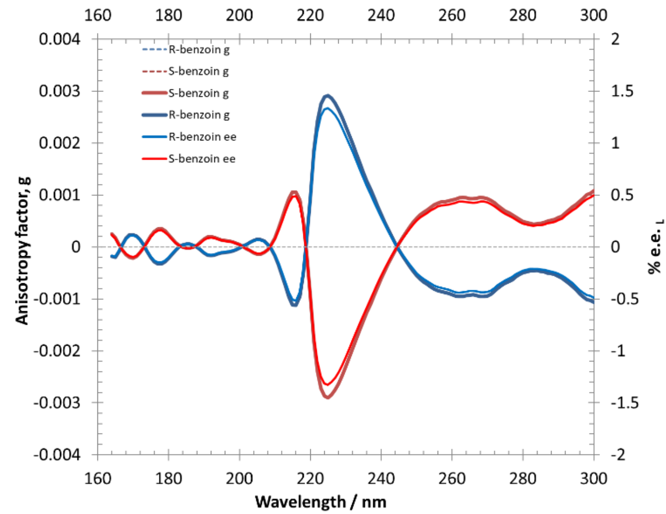
Chiroptical Singatures:

CD & Anisotropy Spectra of Small Molecule Building Blocks/APIs – TD-DFT Approaches



Benzoin





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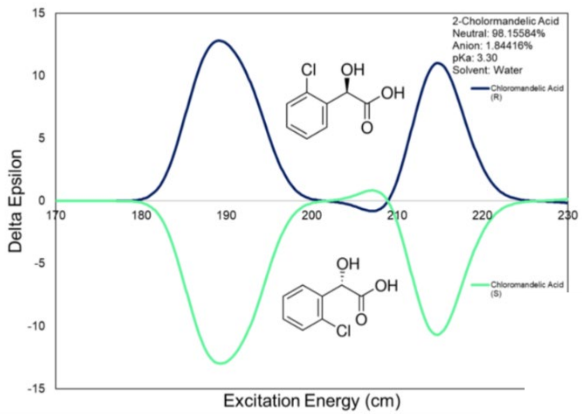
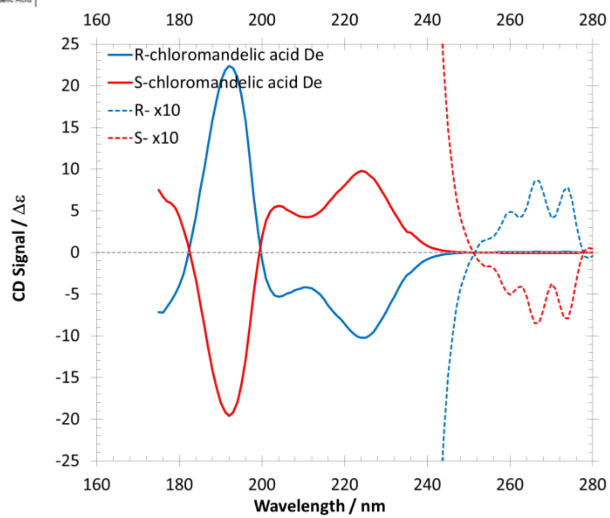
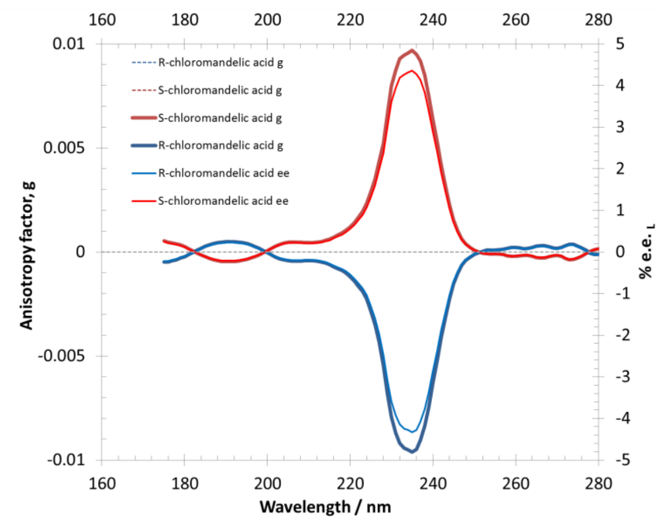
Chiroptical Singatures:
CD & Anisotropy Spectra of Small Molecule Building Blocks/APIs – TD-DFT Approaches



2-Chloromandelic acid





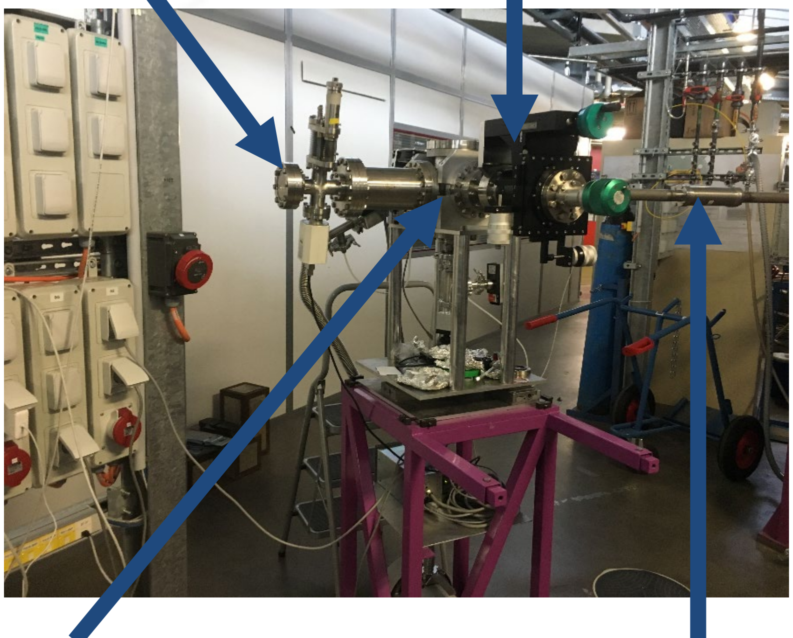
Evans et al.: *Phys. Chem. Chem. Phys.* In preparation.

Chiroptical Induction/Photolysis (Synchrotron SOLEIL, France) :

CPL Asymmetric Photolysis Solution Phase

Alignment Window

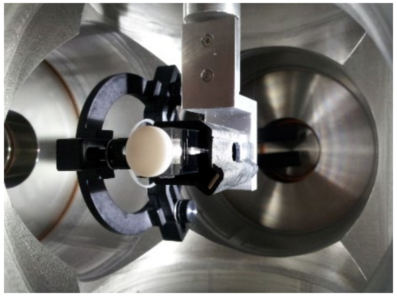
Sample Holder
Alignment Control



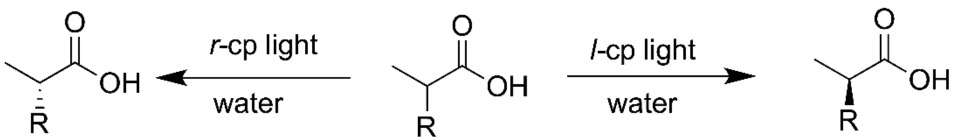
Irradiation Chamber

Beam from Synchrotron

Cuvette Sample Holder for Beam Exposure



Synchrotron SOLEIL

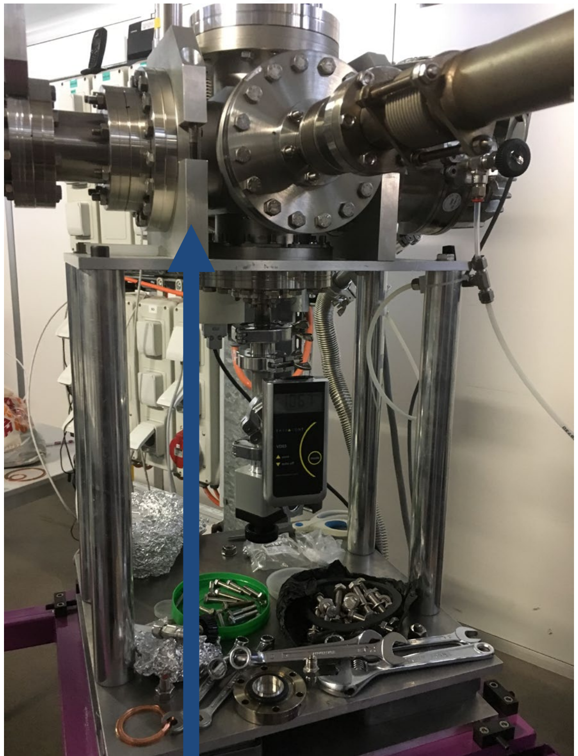


R = -Cl, -OH, $-NH_2$

Evans et al.: *Angew. Chem. Int. Ed.* In preparation.

Chiroptical Induction/Photolysis (Synchrotron SOLEIL, France) :

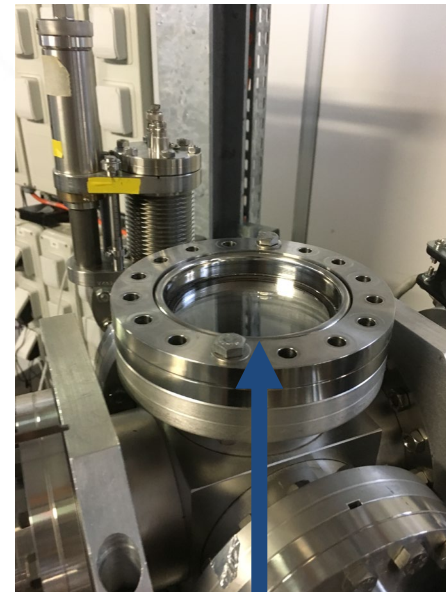
CPL Asymmetric Photolysis
Solution Phase



Sample Irradiation Vacuum Chamber

Beamline

Sample Irradiation Vacuum Chamber

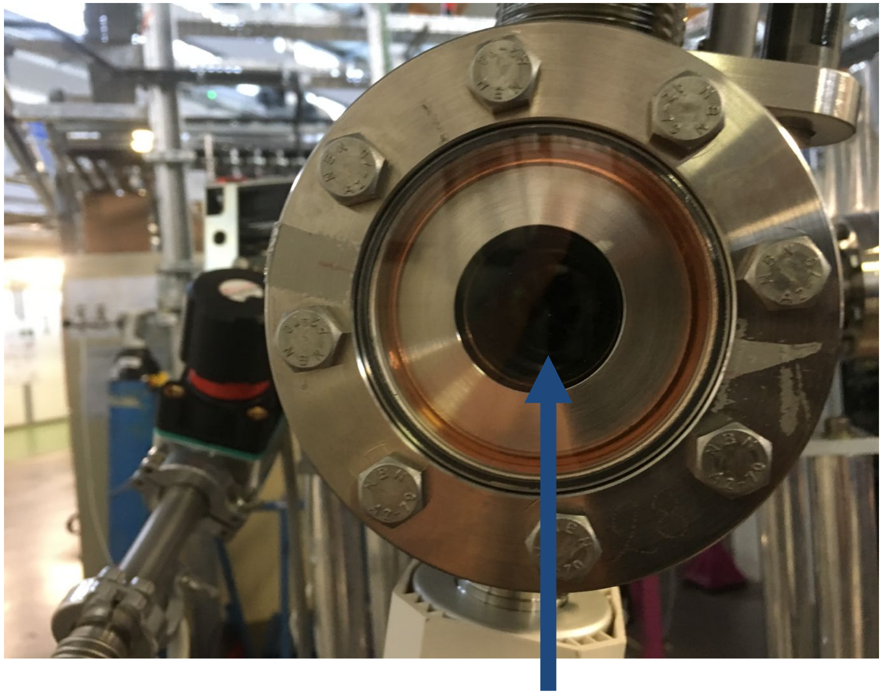


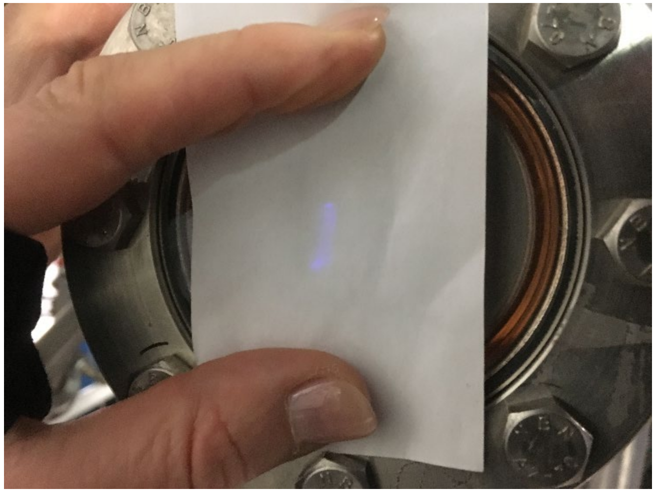
Top of Sample Irradiation Vacuum Chamber

Evans et al.: *Angew. Chem. Int. Ed.* In preparation.

Chiroptical Induction/Photolysis (Synchrotron SOLEIL, France) :

CPL Asymmetric Photolysis Solution Phase





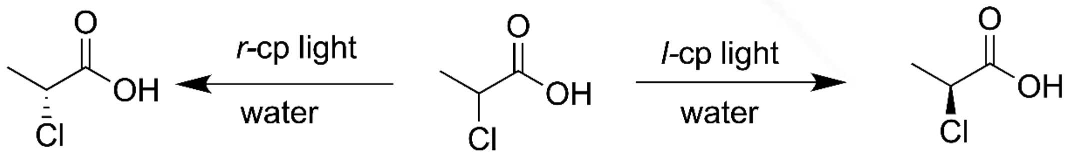
CPL Synchrotron Experiments:
Collaboration with L. Nahon
(Synchrotron SOLEIL, France)
Beamtime awarded 2017, 2018

Evans et al.: *Angew. Chem. Int. Ed.* In preparation.

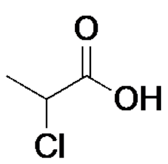
Chiroptical Induction/Photolysis (Synchrotron SOLEIL, France) :

CPL Asymmetric Photolysis
Solution Phase
Batch vs. "Flow"

Experimental Variables:
Batch vs. Flow (4 mL/min.)
Concentrations
Cell Path Lengths
Molecule
Exposure Time
Wavelengths (if Cotton Effect)
Derivatization Technique



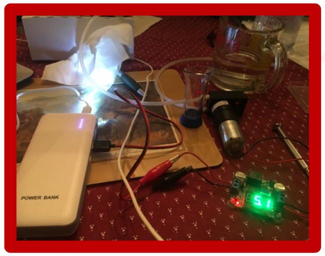
R = -Cl, -OH, $-NH_2$

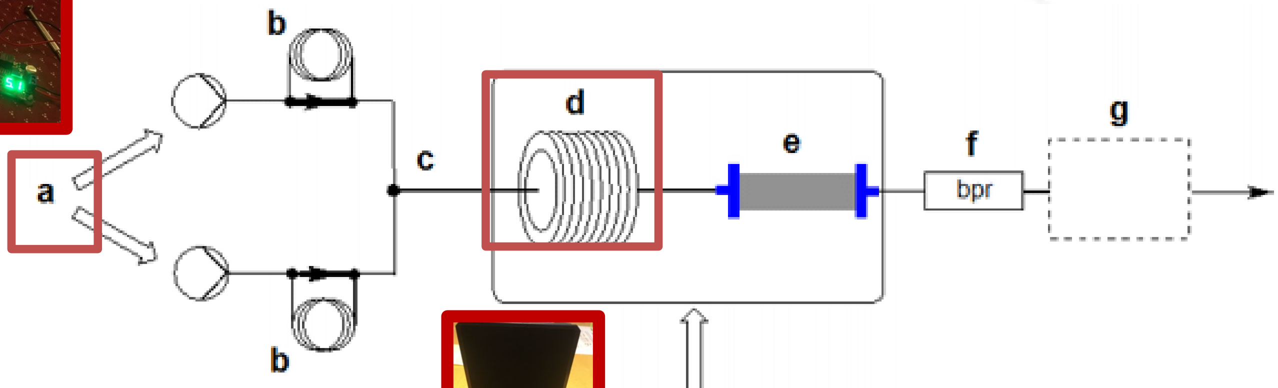
Compound	Irradiation Time (min.)	Irradiation Wavelength (nm/eV)	c (g/mL)	r-cpl/l-cpl	Batch/Flow (mL/min)	Diastereomeric Ratio (S:R)
2-Chloropropionic Acid	None	None	N/A	N/A	N/A	50:50
	60	250/4.96	50	r-cpl	Batch	49:51
	60	250/-4.96	50	l-cpl	Batch	54:46
	60	250/4.96	50	r-cpl	Flow (4 mL/min)	47:53
	60	250/-4.96	50	l-cpl	Flow (4 mL/min)	52:48

Evans et al.: *Angew. Chem. Int. Ed.* In preparation.

Chiroptical Induction/Photolysis (Synchrotron SOLEIL, France) :

CPL Asymmetric Photolysis
Batch vs. "Flow"





-Heat
-Cool
-Oscillator
-Electrochemistry
-Microwave
-Light
-Ultrasound

a. PUMPS

b. REACTION LOOPS

c. T-PIECE

d. COIL REACTOR

e. COLUMN REACTOR/PURIFICATION

f. BACK PRESSURE REGULATOR

g. DOWNSTREAM UNIT
(in-line analytics/work-up)

Darvas F., Dorman G., Hessel V. *Flow Chemistry, Volume 1: Fundamentals*
URL: http://www.organic-chemistry.org/topics/flowchemistry.shtm

Traditional Molecule Making vs. Flow?
A Pictorial History

Traditional Molecule Making vs. Flow?

Time for a Change?

Factor	Continuous	Batch
Cost of factory equipment	High	Low
Rate of production	High	Low
Shut-down times	Rare	Often
Workforce	Few people needed	Many people needed
Ease of automation	Relatively easy	Relatively difficult

Batch Reactor

- Slow temperature control
- Inefficient mass and heat transfer
- Dangerous temperature gradients
- Safety issues for many transformations

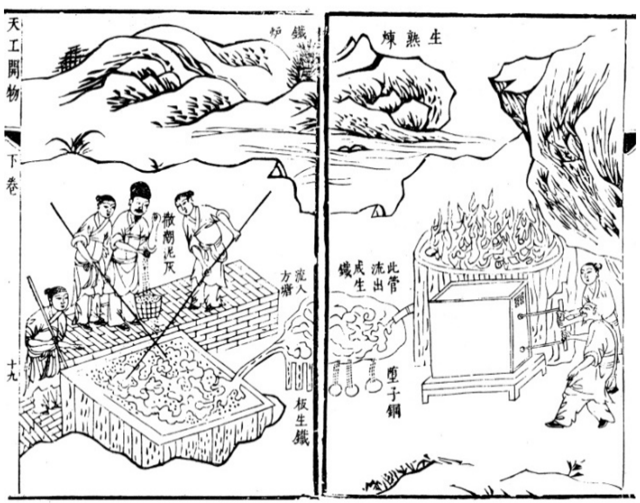
Continuous-Flow Reactor

- Instantaneous heating/cooling
- Very fast mixing (< 1s)
- No concentration/temperature gradients
- Inherently safe

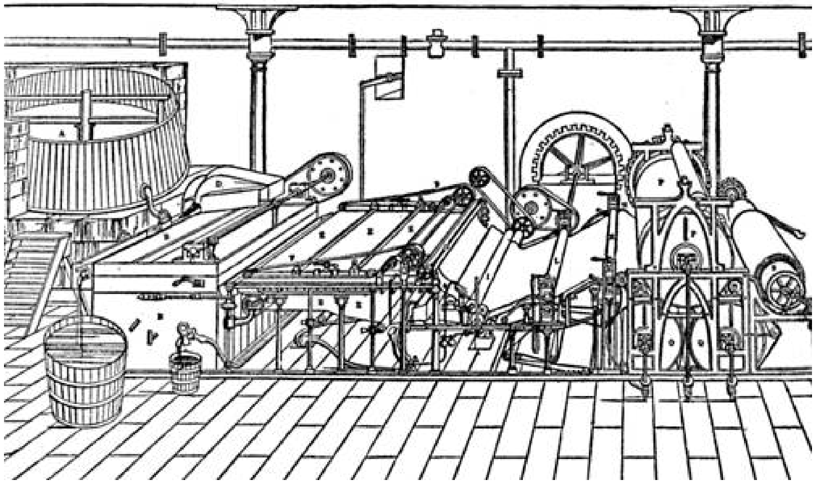
What is "Flow" or Continuous Processing?
A Definition

Continuous processing, or continuous flow processing, is the generation, production, manufacturing or processing of materials without interruption.

Materials in constant motion



Blast furnace used in ancient China, depicted in *Tiangong Kaiwu* encyclopedia, 1637.

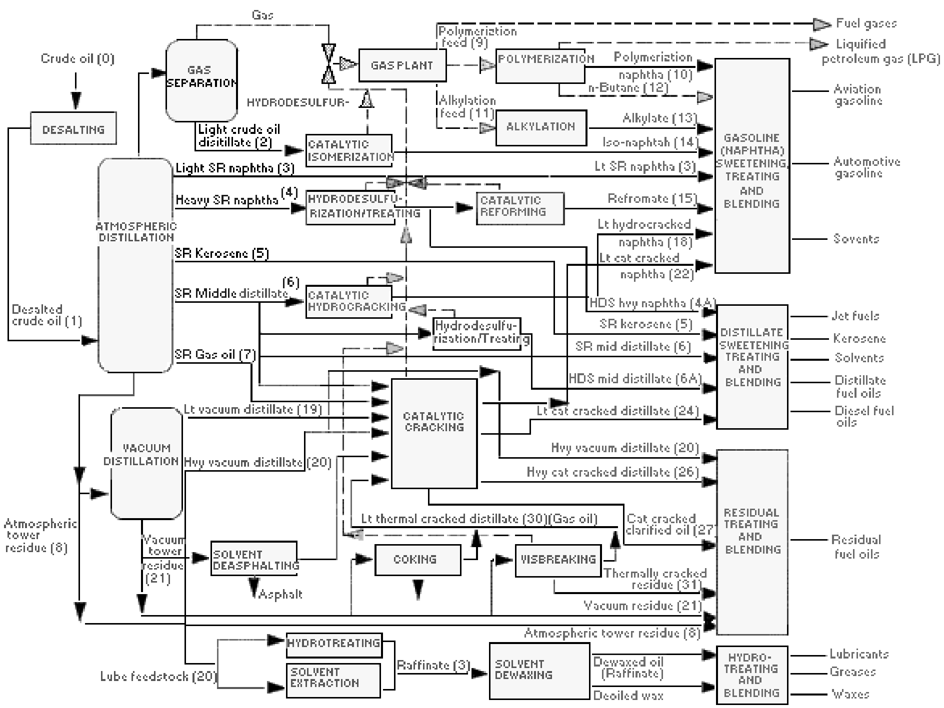


Fourdrinier paper making machine, patented 1799.

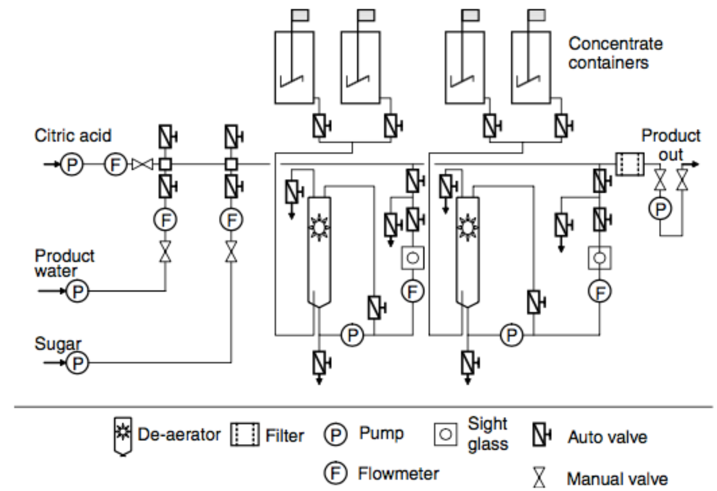
What is "Flow" or Continuous Processing?

Materials in Constant Motion

Petroleum refinery process chart.



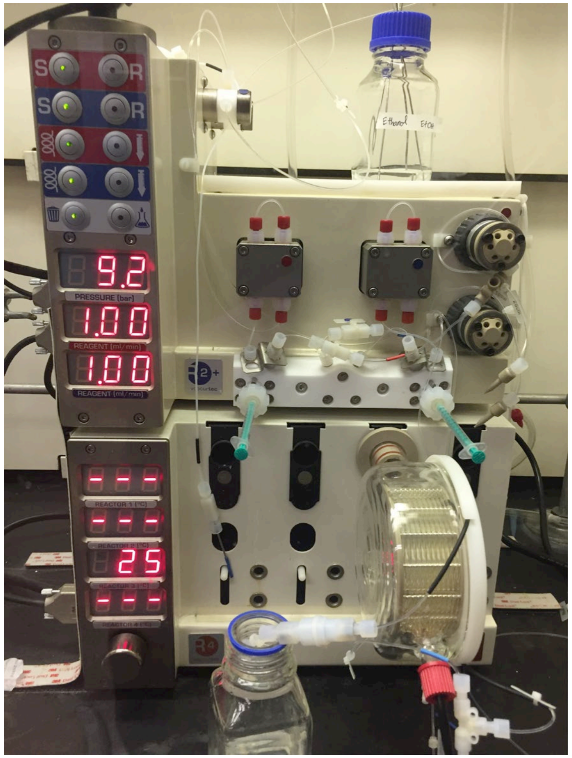
Beverage flavoring process chart. (*Diessel GmbH*)



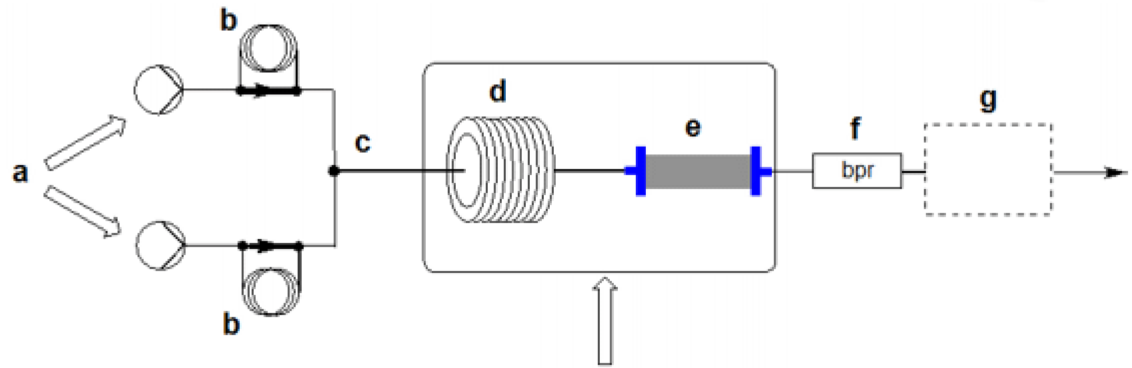
UNCLASSIFIED

Flow/Continuous Processing:
Advantages

- Safer production conditions
- Process of pumping reagents through a reactor tube/coil/pipe/etc.
- Efficient mixing (increased heat/mass transfer)
- Controlled reaction parameters
- Simple automation
- Integrated production and purification
- Consistent reproducibility and scalability
- Smaller reaction vessels
- Previously inaccessible chemistry
- Multiple 'Telescoped' processes possible



Continuous Processing:
Simple Reactor Design



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Flow/Continuous Processing:
State-of-the-Art Synthesis - Reactors

Gas reactor
(http://www.cambridgereactordesign.com/)

Trickle bed reactor
(http://www.helgroup.com/)

Microchip reactor unit
(http://www.chemtrix.com/)

Syringe pumps
(http://syrris.com/)

Gas reactor platform
(http://www.thalesnano.com/)

Reaction platform
(http://www.uniqsis.com/)

Cryogenic reactor unit
(http://www.cambridgereactordesign.com/)

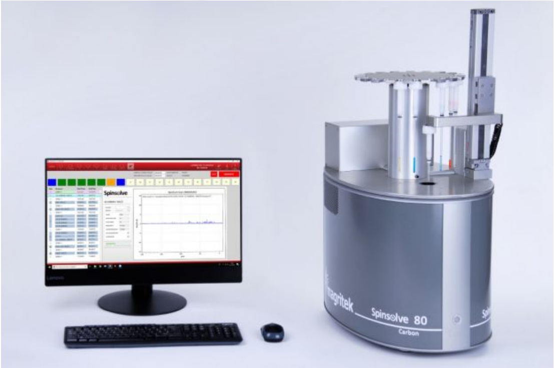
Reaction platform
(https://www.vapourtec.com/)

Reaction platform
(http://www.amtechuk.com/)

Flow/Continuous Processing:
State-of-the-Art Synthesis – Inline Analytics

Flow UV-Vis
(http://www.uniqsis.com/)

React IR
(https://www.mt.com)



Spinsolve Benchtop NMR
(http://www.magritek.com/)

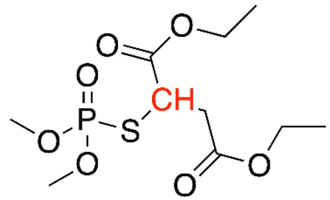
Expression CMS
(https://advion.com)

ReactRaman 785
(https://www.mt.com)

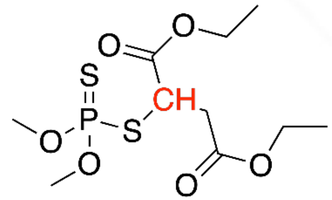
Chiroptical Signatures:

CD & Anisotropy Spectra of OP analogues (and agents) – Establishing the First Experimental Library

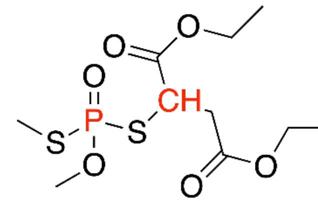
Chirascan CD Spectrometer (LANL)
(https://www.photophysics.com/)



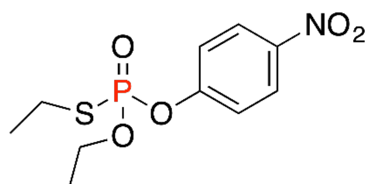
malathion



malaoxon

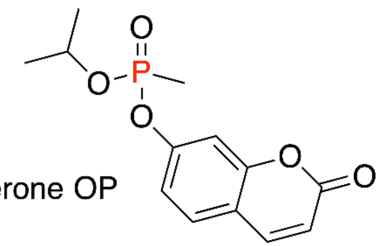


isomalathion



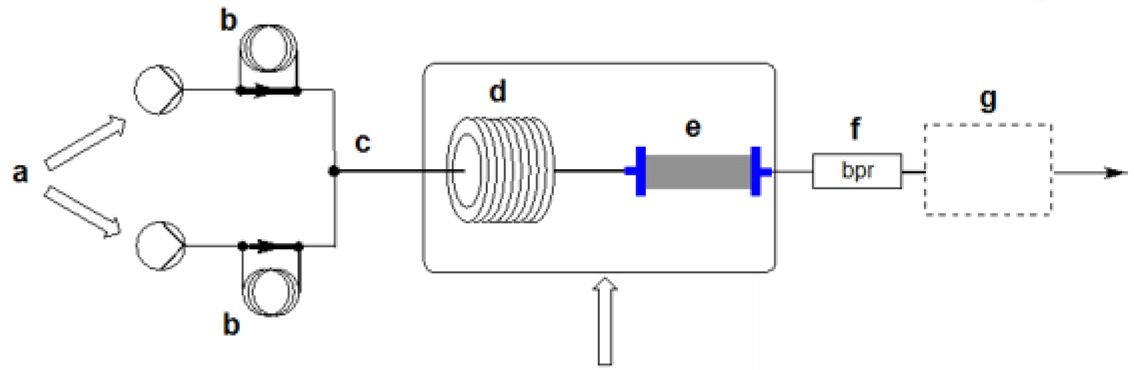
isoparathion

umbelliferone OP



Currently collaborating with Dr. Amanda Neukirch for theoretical predictive CD and anisotropy spectra of OP compounds (T-1, LANL).

Continuous Processing:
Simple Reactor Design



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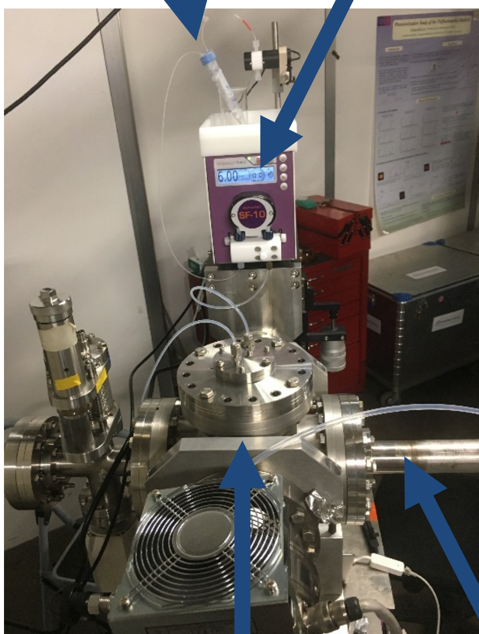
Chiroptical Photocatalyti Destruction of OP Analogues (Synchrotron SOLEIL, France) :

CPL Asymmetric Photolysis
Solution Phase – Flow Conditions

Sample

Pump

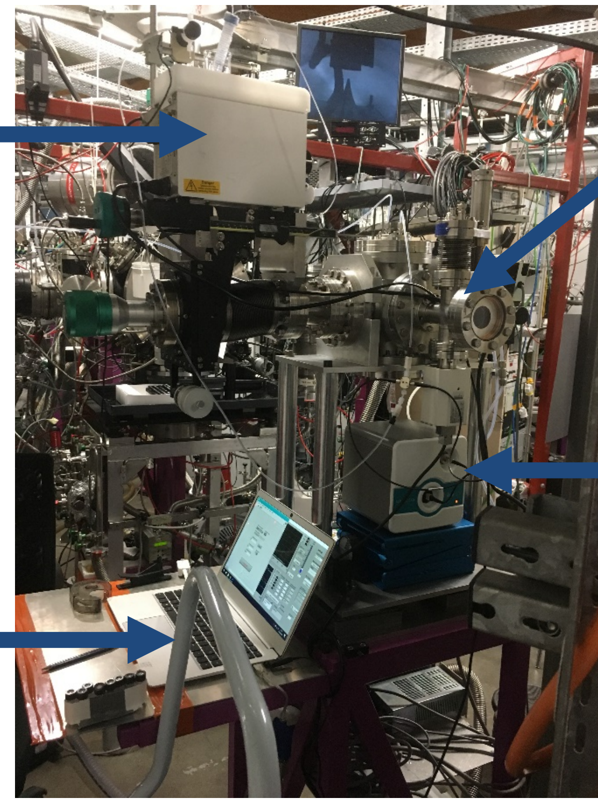


Irradiation Chamber

Beamline

Pump

Software Interface for Pump and Flow UV Control



Irradiation Chamber

Flow UV

Evans et al.: *Angew. Chem. Int. Ed.* In preparation.

Chiroptical Photocatalytic Destruction of OP Analogues (Synchrotron SOLEIL, France) :

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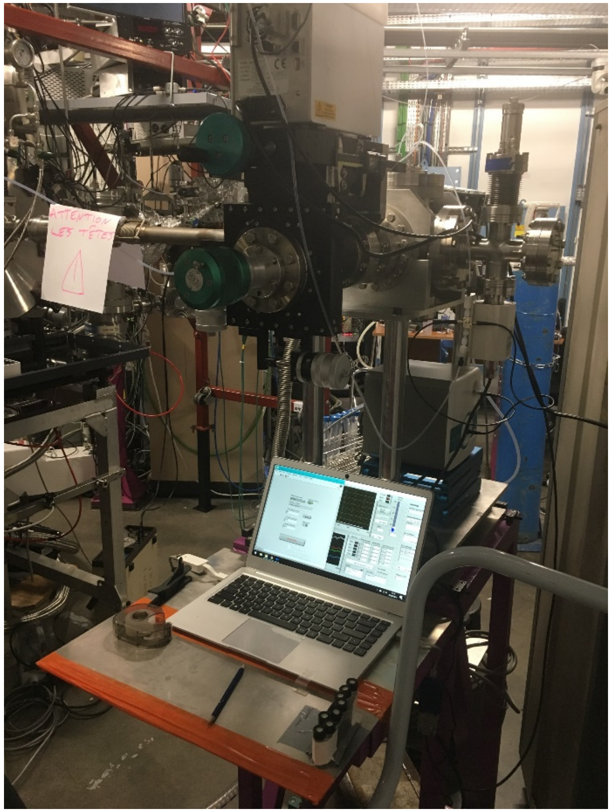
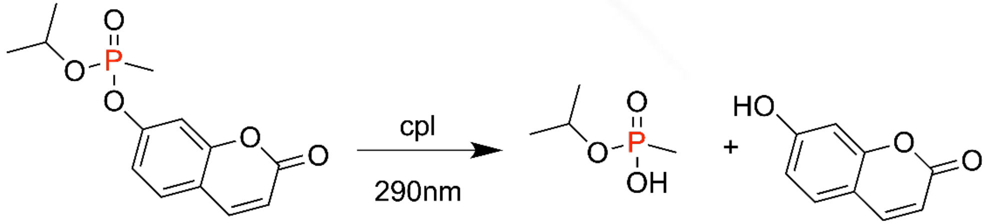
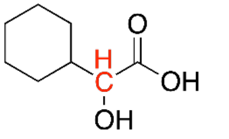
Solution Phase – Flow Conditions

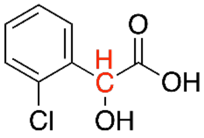




Compound 1



hexahydromandelic acid



2-chloromandelic acid

Experimental Variables:
Flow (6 mL/min.)
Concentrations (0.1, 0.2 mM)
Molecule
Exposure Time (Samples taken every hour)
Wavelengths (if Cotton Effect)

Evans et al.: *Angew. Chem. Int. Ed.* In preparation.

Chiroptical Signatures & Photocatalytic Destruction of Organophosphorus Agents:

Future Directions

- Establish library of experimental/theoretical CD and anisotropy spectra for chiral OP analogues, simulants, & agents (Emerging Threat Lab at LANL):
  - Chirality at P?
  - Chirality at distal C?

- Run further batch/flow experiments at Synchrotron SOLEIL with inline characterization (UV-Vis, FTIR) to optimize conditions for chiroptical photocatalytic destruction of OP analogs/simulants.

- Establish a benchtop system for chiroptical photocatalytic destruction of OP analogs/simulants/agents at LANL.

Current LANL Team: Amanda Evans (B-11), Bob Williams (B-11), Amanda Neukirch (T-1), Aaron Tondreau (C-IIAC), Anatoly Efimov (MPA-CINT), Dmitry Yarotski (MPA-CINT)

“The light…it’s always been there. It will guide you.”
– Maz Kanata, *The Force Awakens*

Other Topics of Interest:
Future Directions

- Continuous Biocatalysis: Use of immobilized enzymes or whole cells as catalysts under continuous flow conditions.
  Green manufacturing, solvent recycling – for fuel/propellant generation

- Manufacturing in Microgravity: Use of microfluidic approaches for on-demand generation of chemical products.
  Making chemicals as needed in remote regions (war zones?)

- Continuous Flow Signatures: Forensics of Flow Manufacturing of CB agents?
  Characterization of flow approaches for making threats

Please do ask me more about any of these topics.

Thank you for your Attention ☺

Acknowledgements:

Collaborators:
Professor S. Ley & Group (University of Cambridge, UK)
Professor F. Arnold & Group (California Institute of Technology, USA)
Professor C. C. Wang & Group (University of Southern California, USA)
Professor N. Kotov & Group (University of Michigan, USA)
Dr. S. Hoffmann (ISA, Aarhus University, Denmark)
Dr. L. Nahon (Synchrotron SOLEIL, France)
Professor G. Weiss (UC Irvine, USA)
Professor C. Raston (Flinders University, Australia)