Atom Economy, Biodegradation, Catalysis, and Green Toxicology: Tools for the Delivery of Sustainable Chemistry based on Ionic Liquids

Prof. Nicholas Gathergood
ERA Chair of Green Chemistry

Tallinn University of Technology, Estonia

Oslo, June 2017

12 Principles of Green Chemistry

1. Prevent waste
2. Atom Economy
3. Less Hazardous Chemical Syntheses
4. Designing Safer Chemicals
5. Safer Solvents and Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstock's
8. Reduce Derivatives
9. Catalysis (vs. Stoichiometric)
10. Design for Degradation
11. Real-time analysis for Pollution Prevention
12. Inherently Safer Chemistry for Accident Prevention

P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998

Three Tiers of Assessment

Toxicity

Biodegradation

Bioaccumulation

PERSISTENCE OF ‘TOXIC’ CHEMICALS

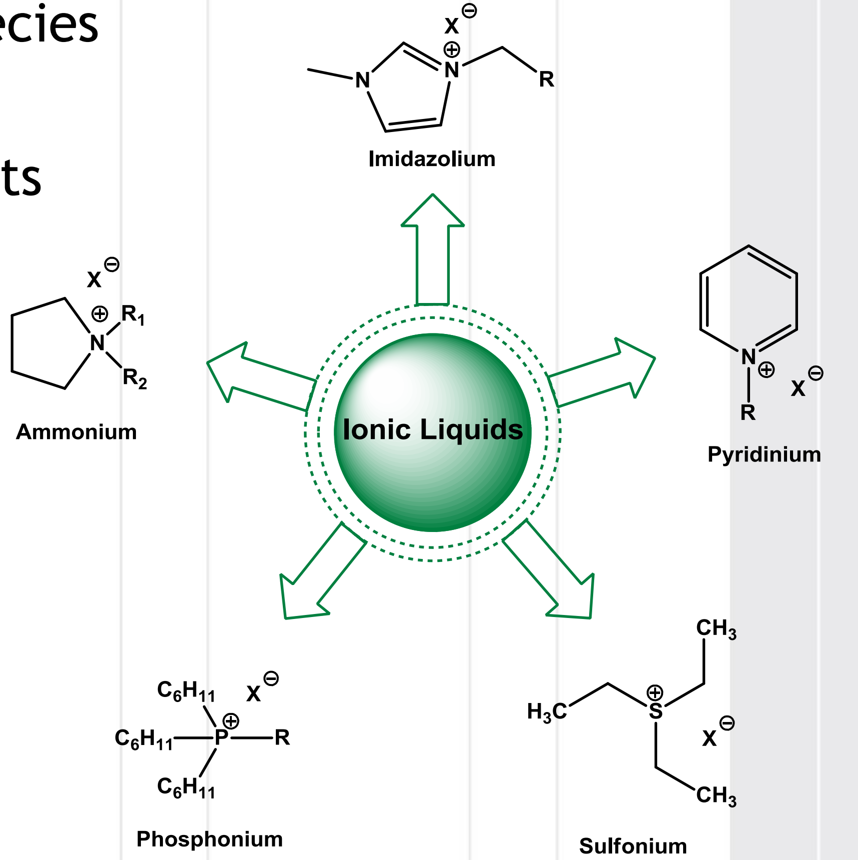
Ionic Liquids

Poorly coordinated ionic species

Most often low melting points (<100 °C)

Properties:

Highly solvating
Non-flammable
Low vapour pressure
High thermal stability
Large liquid range



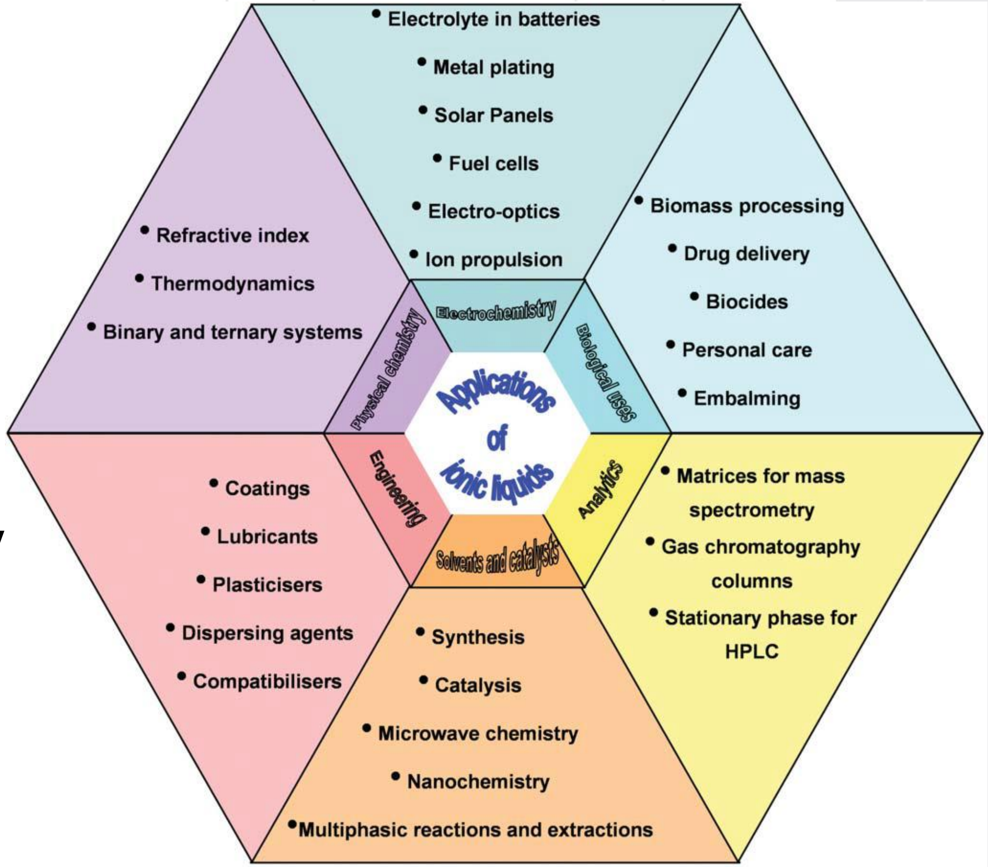
X = Br, Cl, BF_4, PF_6, $OctOSO_3$, $N(CN)_2$, NTf_2 etc

Ionic Liquids

Suitable for a range of organic reactions and provide:

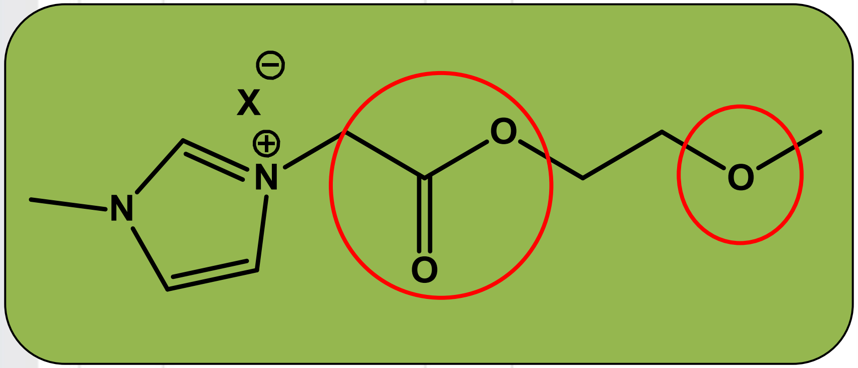
Control of product distribution
Enhanced rate/or reactivity
Ease of product recovery
Catalyst immobilisation
Recyclability

Green alternatives to VOCs?



Seddon *et al. Chem. Soc. Rev.*, 2008, **37**, 123-150

Designing Biodegradable ILs



X = Br, NTf_2, BF_4, Octyl sulfate, PF_6, $N(CN)_2$

Gathergood and Scammells, *Aus. J. Chem.* 2002, **55**, 557

Gathergood, Garcia and Scammells, *Green Chemistry*, 2004, **6**,166

Garcia, Gathergood and Scammells *Green Chemistry*, 2005, **7**, 9

Gathergood, Scammells and Garcia, *Green Chem.*, 2006, **8**,156

Gathergood *et al. Green Chem.*, 2009, ***11***, 466 & 475

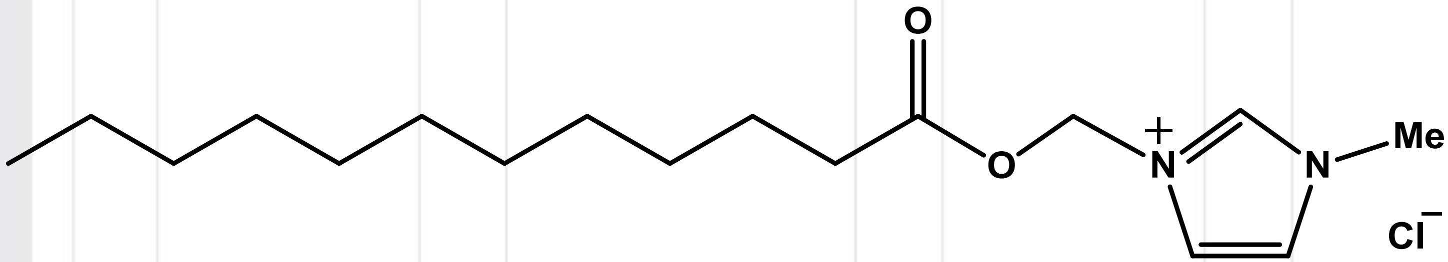
Coleman and Gathergood, *Chem. Soc. Rev.*, 2010, ***39***, 600

Jordan and Gathergood *Chem. Soc. Rev.*, 2015,**44**, 8200

PCT/EP2008/060978 & PCT/EP2010/052345

Effect of introduction of oxygen (i.e. ester/amide) on biodegradability and toxicity

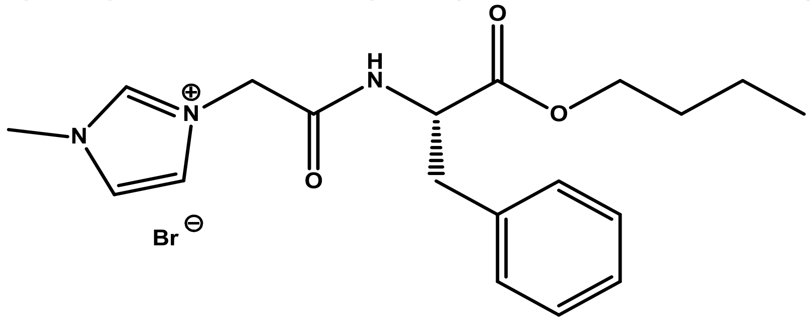
Soft Antimicrobials



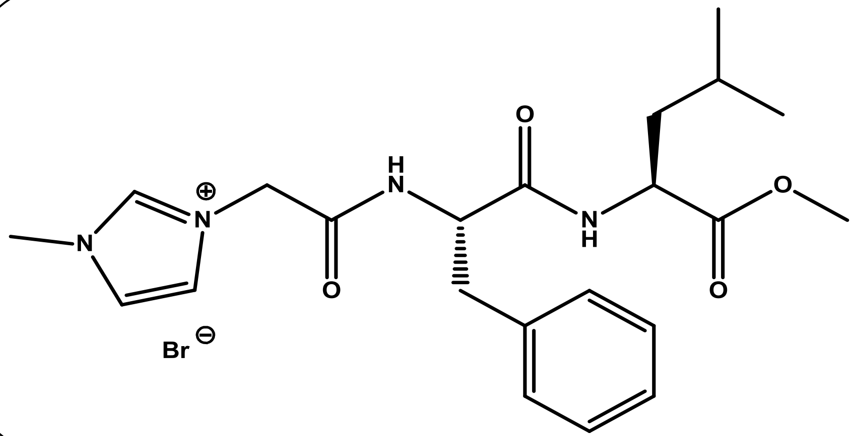
Effective at ppm concentrations

Bodor et al. *J. Med. Chem.* **1980**, *23*, 469, 474 & 566.

Amino acid based ILs



Readily
Biodegradable
CO_2 headspace test
61%, 28 days



Readily
Biodegradable
CO_2 headspace test
64 %, 28 days

Low toxicity towards clinically relevant bacteria strains or fungi screened against

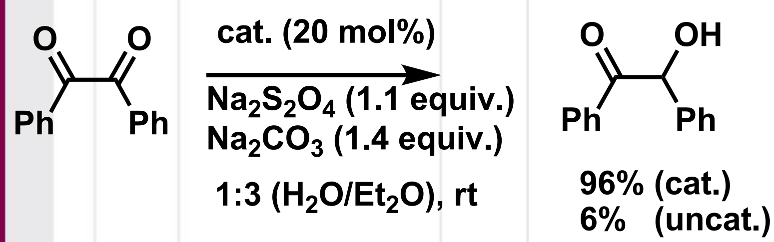
D. Coleman, M. Špulák, M. T. Garcia and N. Gathergood, *Green Chem.*, 2012,**14**, 1350

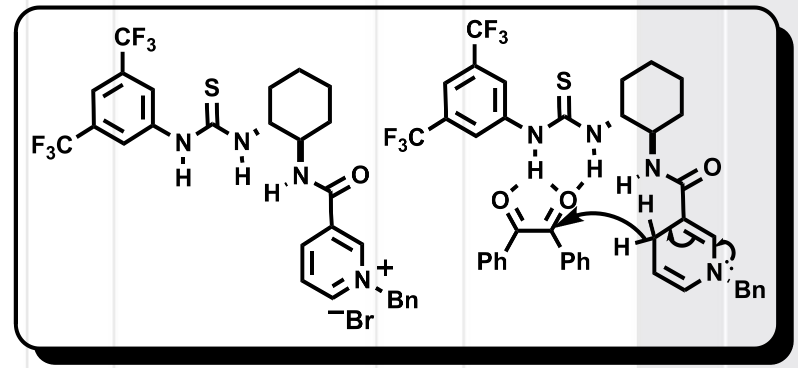
Amino acid based ILs

- **Head Group**
- **Amide Bond**
- **Side Chain**

Unexpected Catalysis

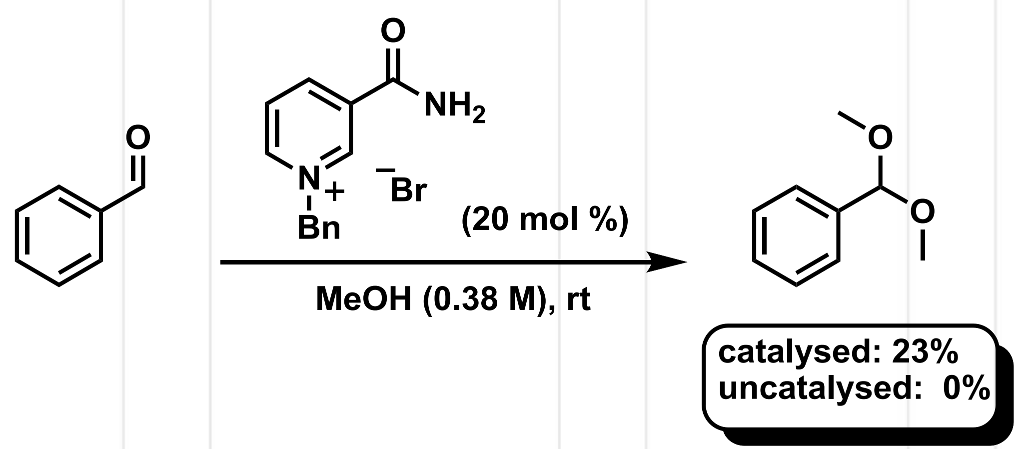
Earlier study: thiourea catalysis of ketone reduction





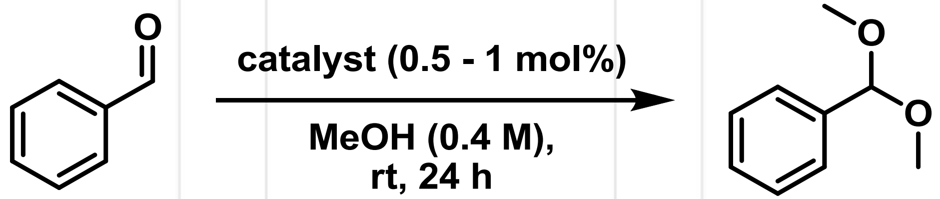
Unusual observation:

acetal protection of benzaldehyde in the <u>absence</u> of an acid

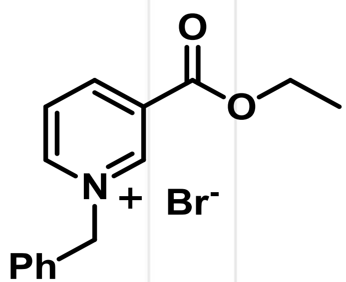


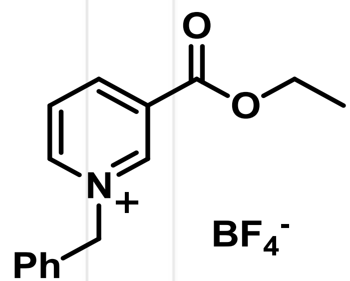
Connon *et al. Org. Lett.*, **2008**, 10, 4935-4938

Pyridinium Catalysis



Acetalisation of benzaldehyde:

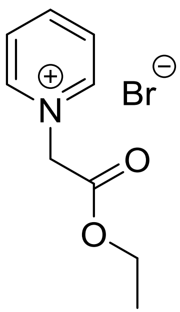


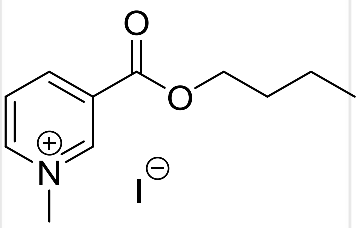


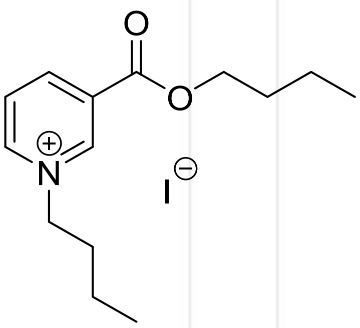
1 mol%:	**90% Yield**	**1 mol%:**	**95% Yield**
0.5 mol%:	**35% Yield**	**0.5 mol%:**	**81% Yield**

Procuranti, B.; Myles, L.; Gathergood, N.; Connon, S. J. *Synthesis*, **2009**, 23, 4082-86.

Effect of ester group







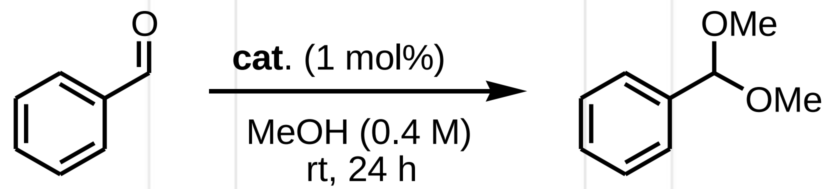
CBT 87 %

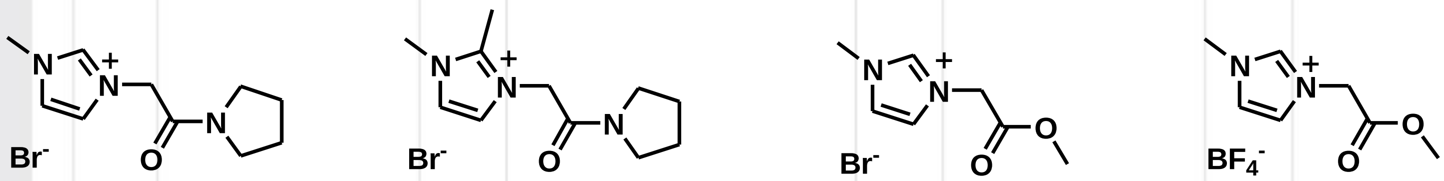
72 %

84 %

Change heterocycle from pyridinium to imidazolium
Introduce EWGs, esters (c.f. amides)

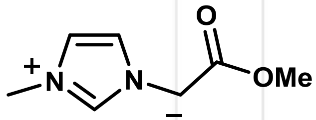
1st Gen Imidazolium Catalysis

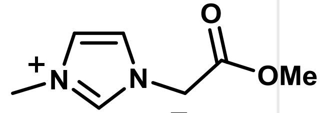


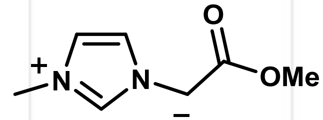


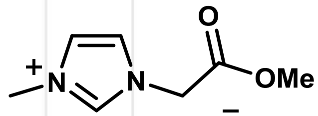
14% Yield | 11% Yield | 12% Yield | 86% Yield

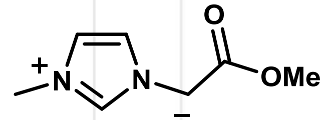
Gathergood, N. and Connon, S. J. et al.
Green Chemistry, **2010**, 12, 1157-1162.

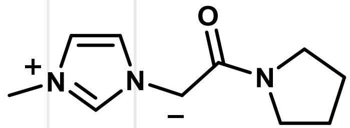

9 Br^-

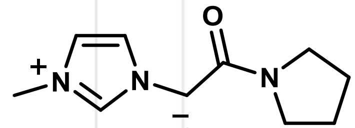

10 BF_4^-

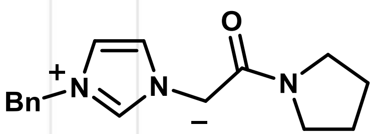

11 NTf_2^-

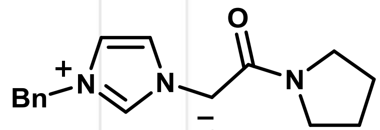

12 $C_8H_{17}SO_4^-$

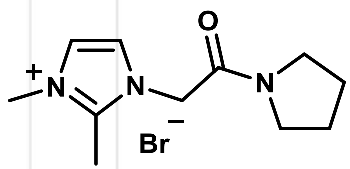

13 PF_6^-


14 Br^-


15 NTf_2^-


16 Br^-


17 NTf_2^-



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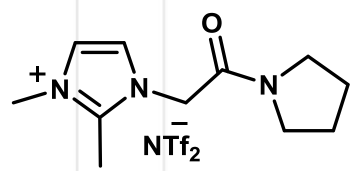

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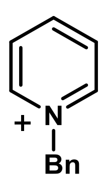
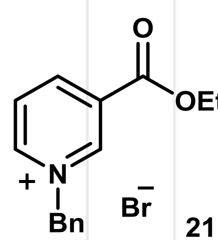
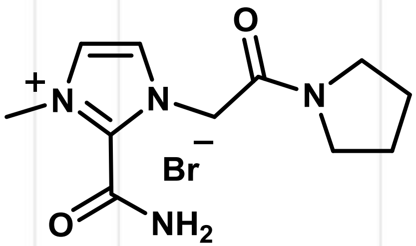

Br^- 20


Br^- 21



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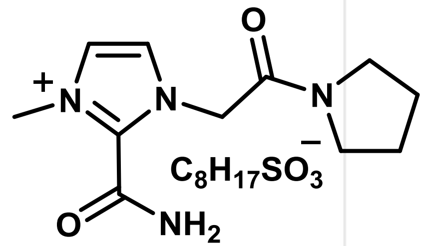

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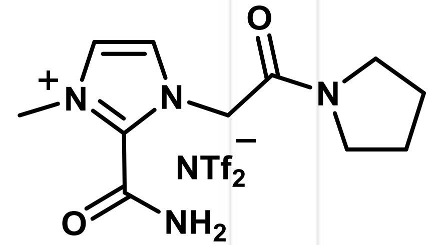

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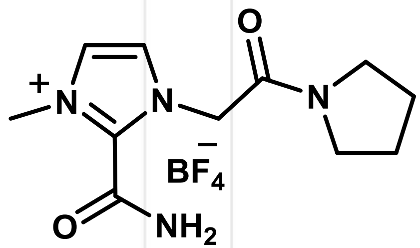

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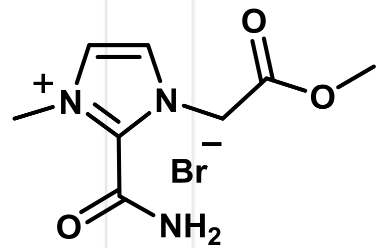

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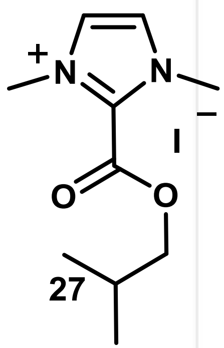

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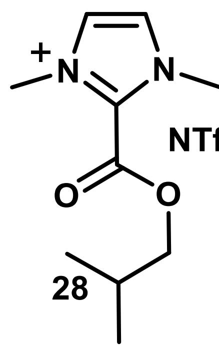

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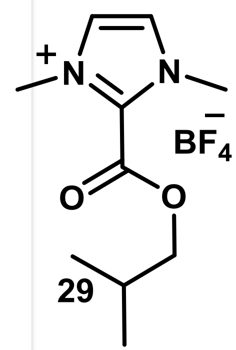

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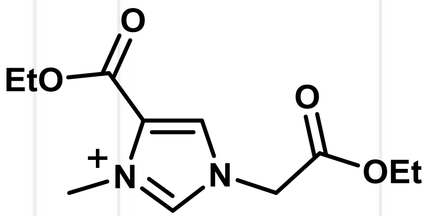
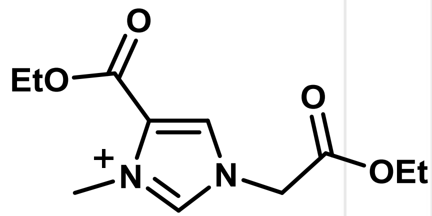
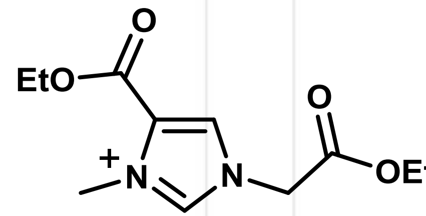


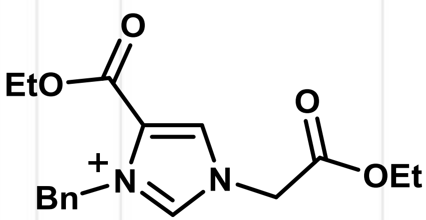
30 Br^-



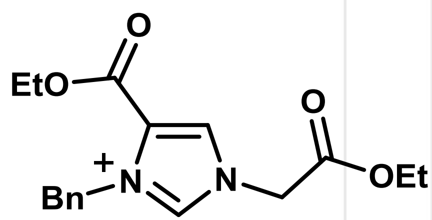
31 I^-



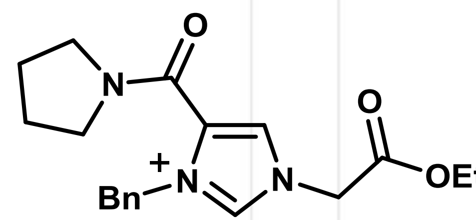
32 BF_4^-



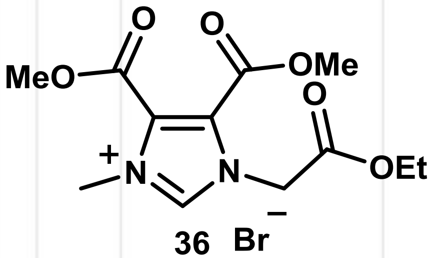
33 Br^-



34 BF_4^-

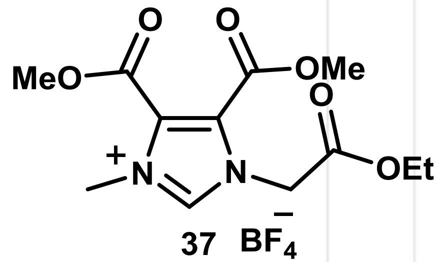


35 Br^-



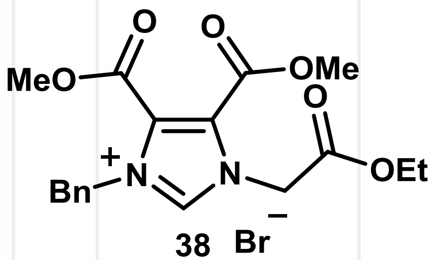
MeO
O
O
OMe
O
OEt
N
N
Br

36



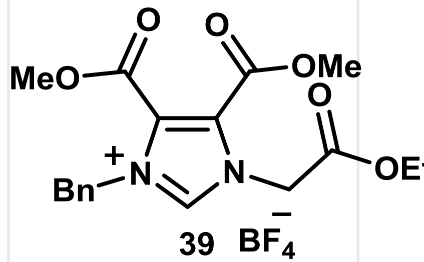
MeO
O
O
OMe
O
OEt
N
N
BF4

37



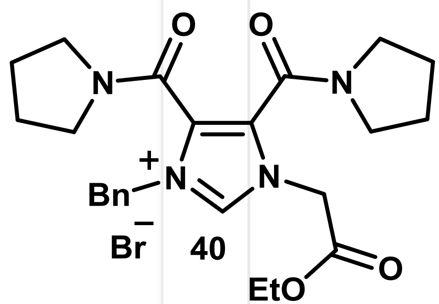
MeO
O
O
OMe
O
OEt
Bn
N
N
Br

38



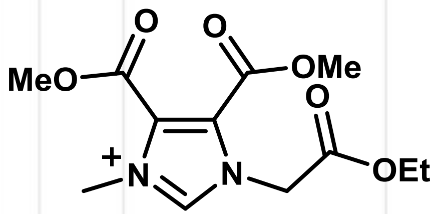
MeO
O
O
OMe
O
OEt
Bn
N
N
BF4

39

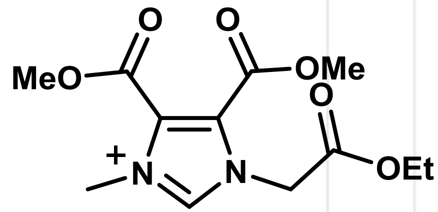


O
O
N
N
Bn
N
N
Br
EtO
O

40



36 Br^-



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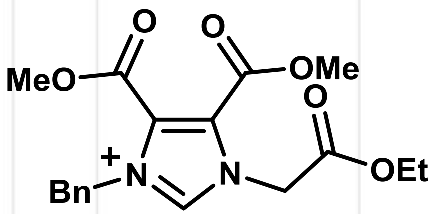
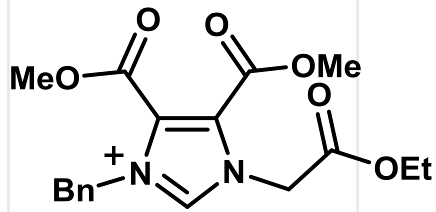


38 Br^-



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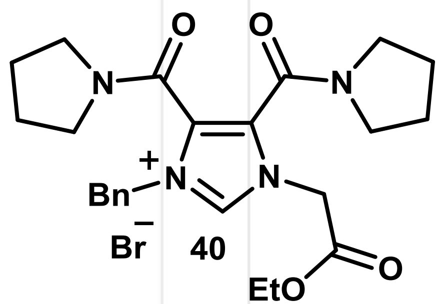
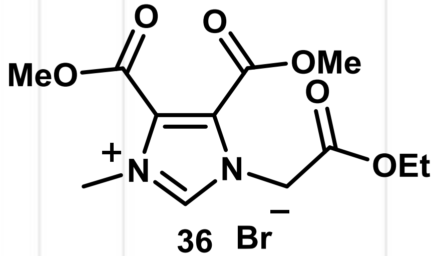


Br^- 40

Green Metrics Lab Book Spreadsheet (Lapkin and BRITEST)



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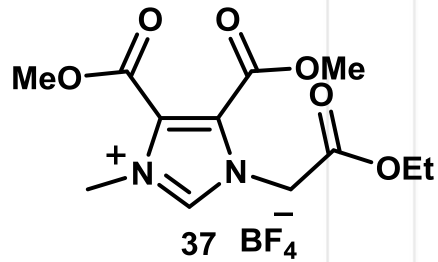

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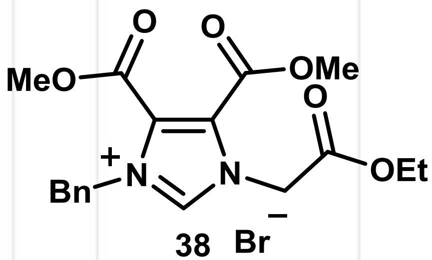

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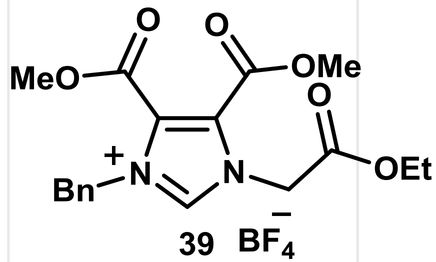

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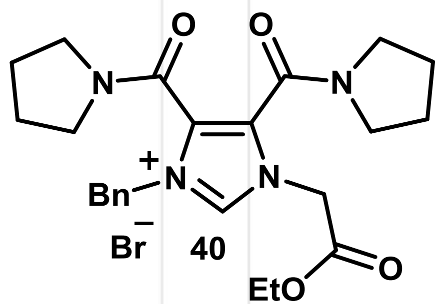

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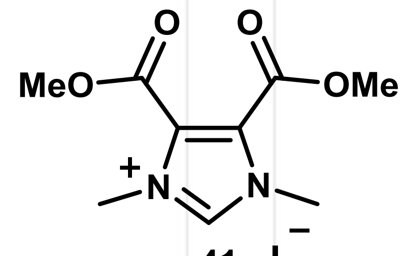

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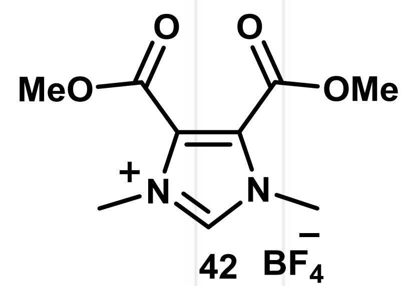

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Green Metrics Lab Book Spreadsheet (Lapkin and BRITEST)

Green Chemistry Metrics

Atom Economy

Hydrogenation of cyclohexene

Alkylation of Pyridine

Ester Hydrolysis

Green Chemistry Metrics

Atom Economy

Hydrogenation of cyclohexene

Alkylation of Pyridine

Ester Hydrolysis

BRITEST Project

Green Chemistry Metrics

Atom Economy

Hydrogenation of cyclohexene

Alkylation of Pyridine

Ester Hydrolysis

BRITEST Project

Green Chem., 2015, **17**, 3111-3121

Table 14 Proposed 'Traffic Light' system to applied to salts **9–42**

Salt	Cat. Act.	Cat. Syn. (NS)	Cat. Syn. (AAE)	Tox. Bac.	Tox. Fung.	Biodeg.
9	R	G	G	G	G	R
10	R	G	G	G	G	R
11	R	G	G	G	G	*R*
12	R	G	G	G	G	*A*[a]
13	R	G	G	G	G	*R*
14	R	G	A	G	G	R
15	R	A	A	G	G	*R*
16	R	G	A	G	G	R
17	R	A	A	G	G	*R*
18	R	G	A	G	G	R
19	R	A	A	G	G	*R*
20	nr[b]	A	A	G	G	R
21	A	A	A	G	G	A
22	R	A	A	G	G	R
23	R	R	A	G	G	*R*
24	R	R	A	G	G	*A*[a]
25	R	R	A	G	G	R
26	R	A	A	G	G	R
27	R	G	A	G	G	A
28	R	A	A	G	G	*A*
29	A	G	A	G	G	A
30	A	A	R	G	G	R
31	A	A	*R*	G	G	*R*
32	A	A	R	G	G	R
33	A	A	R	G	G	*R*
34	A	A	A	G	G	*R*
35	A	A	*R*	G	G	R
36	A	A	A	A	G	*A*
37	G	R	R	G	G	A
38	A	R	R	A	G	A
39	G	R	R	A	G	R
40	A	R	A	G	G	R
41	A	A	A	A	A	R
42	G	A	R	G	G	R

[a] ($OctSO_4$ salt). [b] nr = no reaction at 20 mol% loading. Entries in italics are estimated. NS = number of synthetic steps, AAE = Average Atom Economy.

Key for Traffic Signal Light Classification in Table

Catalyst Activity (Cat. Act.)
Green: ≥90% yield with 0.1 mol% catalyst loading
Amber: ≥90% yield with 1 mol% catalyst loading
Red: <90% yield with 1 mol% catalyst loading

Catalysts Synthesis
(Cat. Syn., Number of steps, NS)
Green: <3
Amber: 3
Red: >3

Catalysts Synthesis
(Cat. Syn., Average Atom Economy, AAE)
Green: 1–0.85
Amber: 0.85–0.70
Red: <0.70

Antibacterial Toxicity (Tox. Bac.)
Green: >2 mM all strains, or up to solubility limit
Amber: MIC 0.25–2.0 mM
Red: MIC <0.25 mM

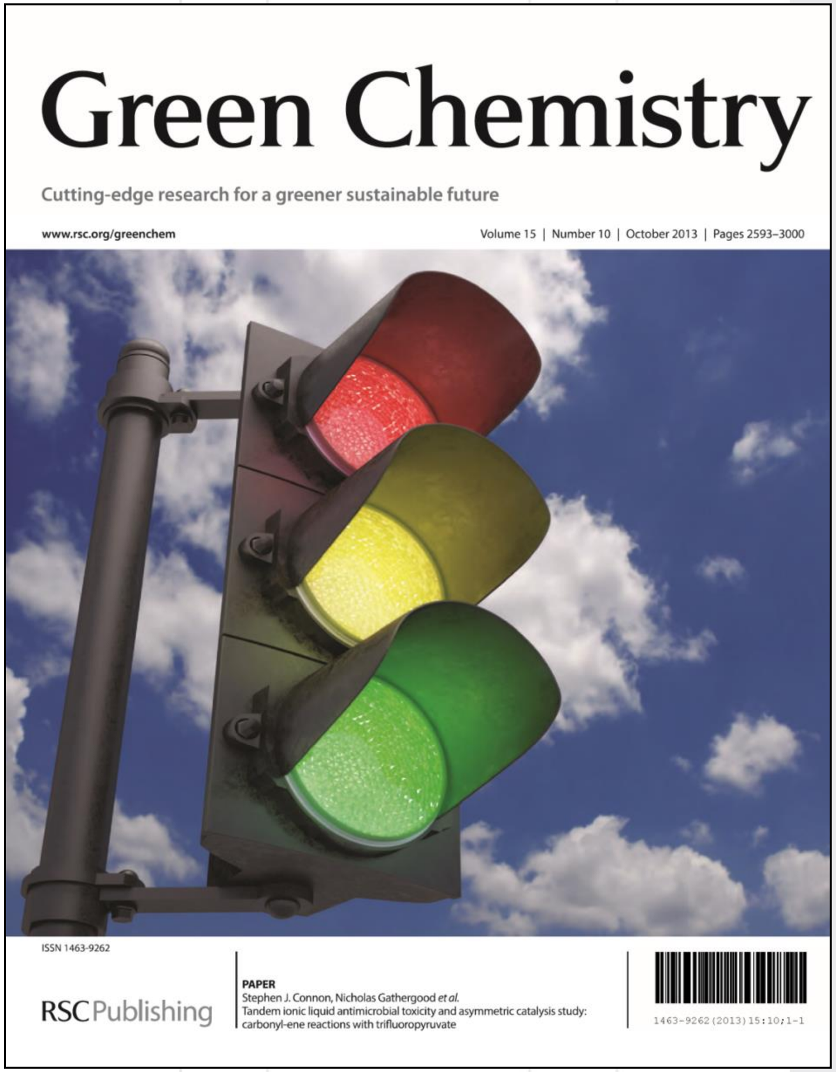
Antifungal Toxicity (Tox. Fung.)
Green: >2 mM all strains, or up to solubility limit
Amber: MIC 0.25–2.0 mM
Red: MIC <0.25 mM

Biodegradation (Biodeg.)
Green: 60+% Readily Biodegradable
Amber: 20–59%
Red: 0–19%

Gore, Myles, Spulak, Beadham, Garcia,
Connon, Gathergood,
Green Chem., **2013**, 15 (10), 2727 – 2739.

Myles, Gore, Gathergood, Connon,
Green Chem., **2013,** 15 (10), 2740 - 2746.

Gore, Truong, Pour, Myles,
Connon, Gathergood,
Green Chem., **2013**, 15 (10), 2747 - 2760



Gore, Myles, Spulak, Beadham, Garcia,
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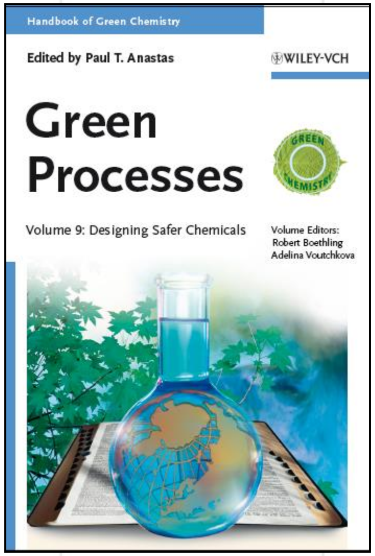

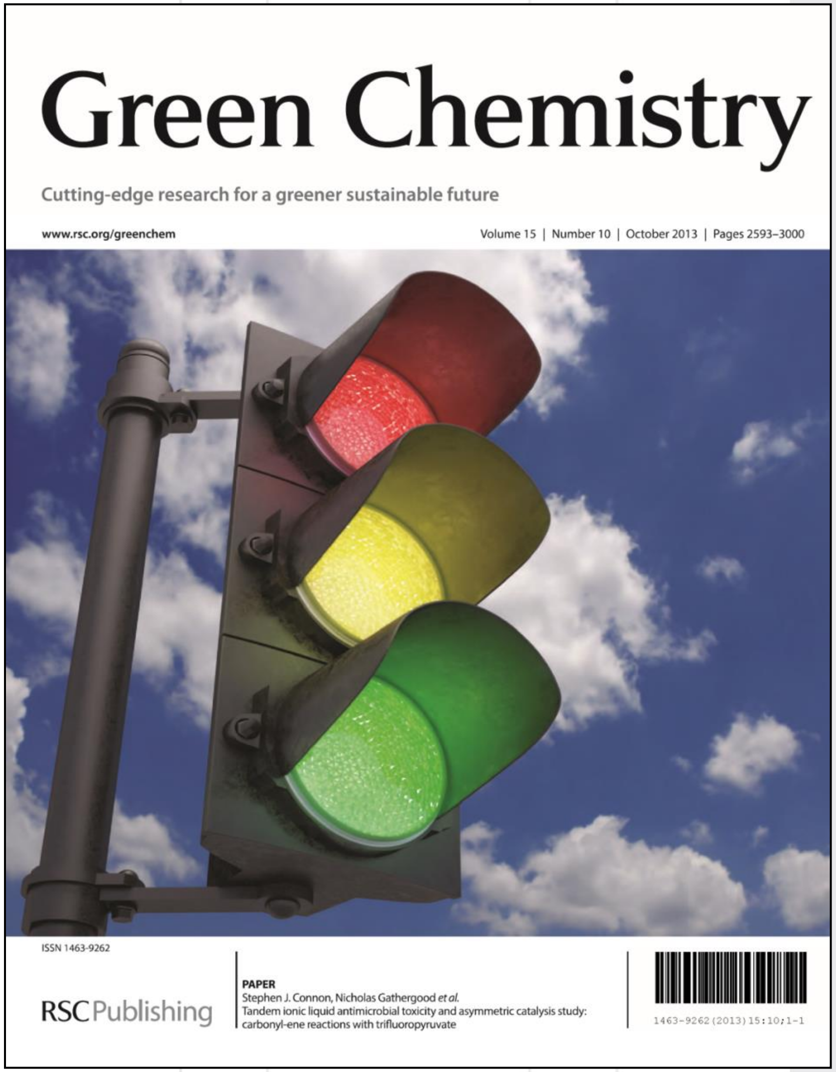

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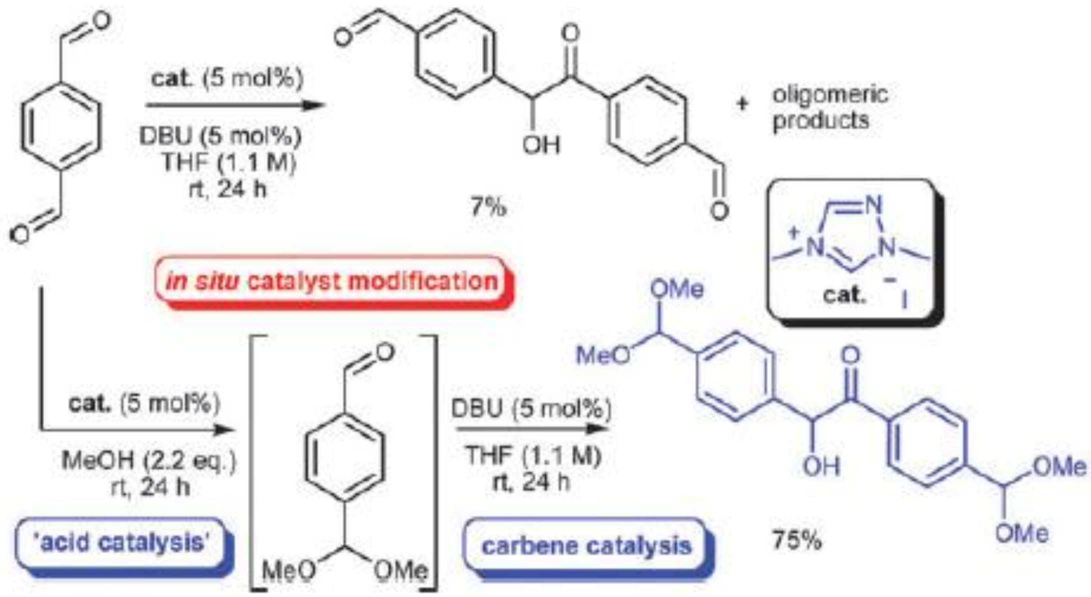


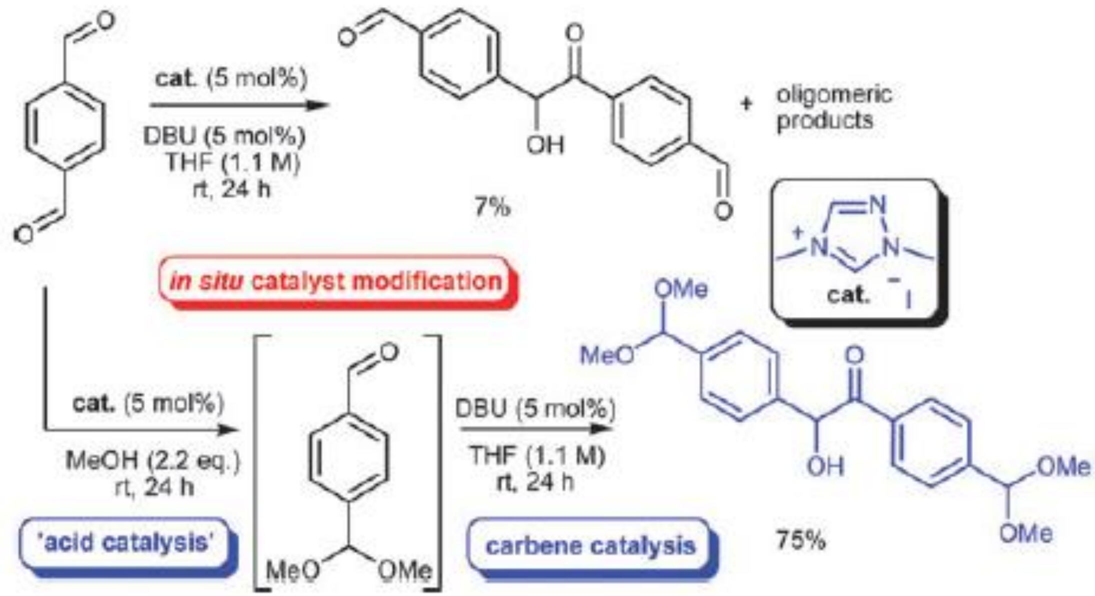
The catalytic versatility of low toxicity dialkyl-triazolium salts: *in situ* modification facilitates diametrically opposed catalysis modes in one pot

Lauren Myles, Nicholas Gathergood* and Stephen J. Connon*

A triazolium salt can serve as a precatalyst for both a strong acid and a powerful base/nucleophile simultaneously (depending on the additive employed) which allows a unique *in situ* modification strategy in which the role played by the catalyst is sequentially controlled in an 'on–off' fashion.

Chem. Commun., 2013, 49 (46), 5316

Just an Acid Catalyst?



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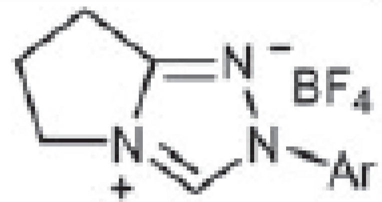
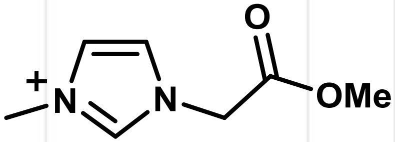
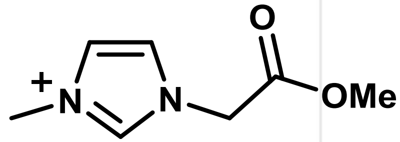


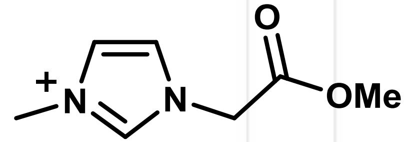
19 Ar = C_6F_5



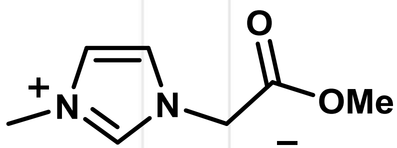
9 Br^-



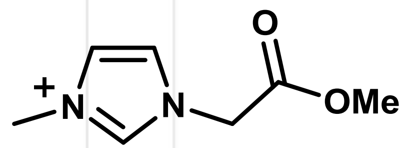
10 BF_4^-



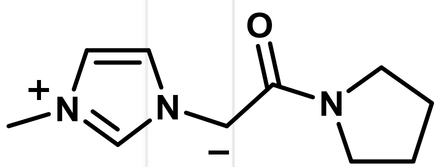
11 NTf_2^-



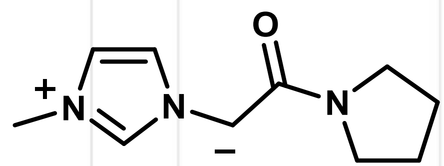
12 $C_8H_{17}SO_4^-$



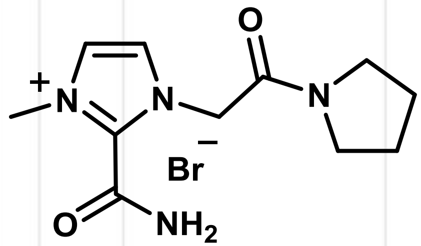
13 PF_6^-



14 Br^-



15 NTf_2^-



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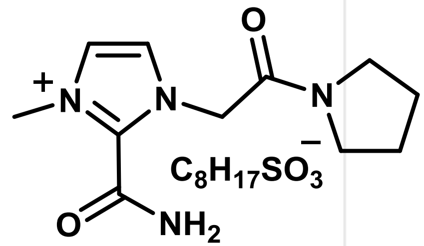

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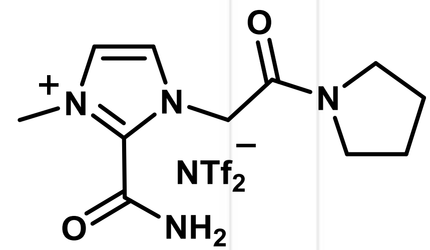

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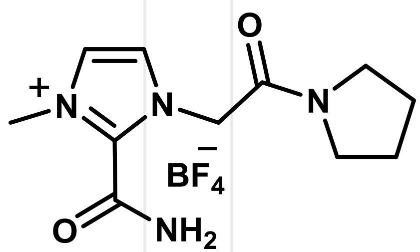

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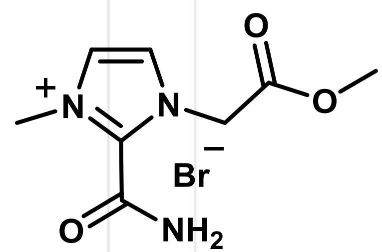

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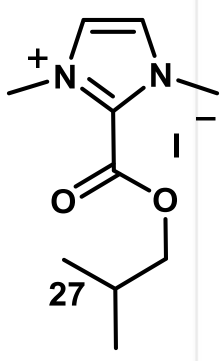

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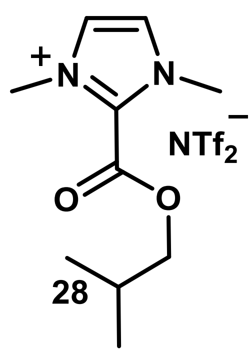

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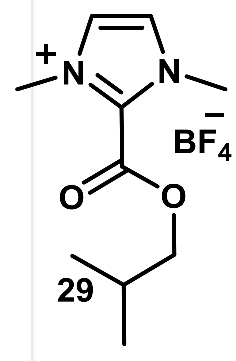

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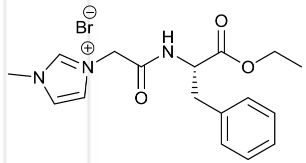

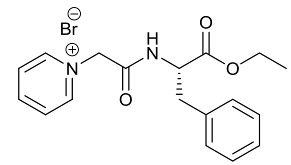

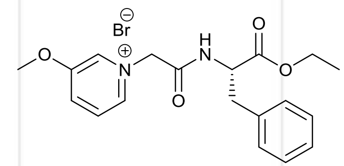

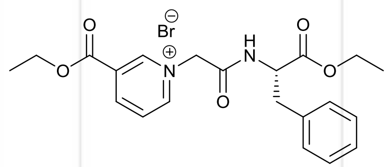

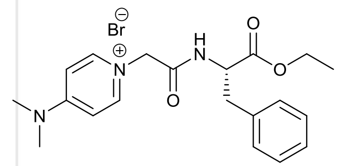

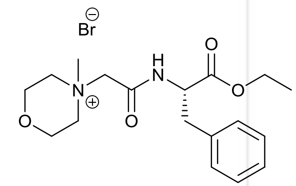

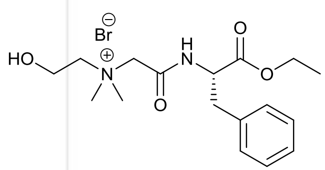

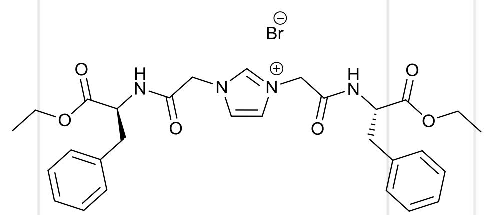

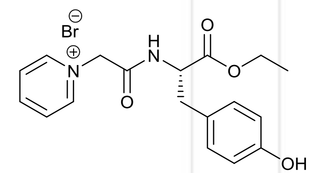

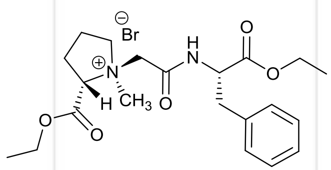

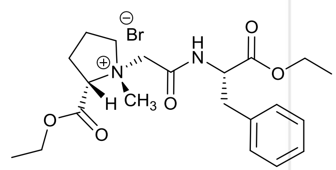

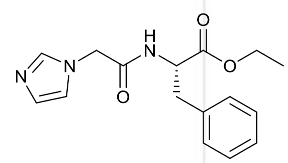

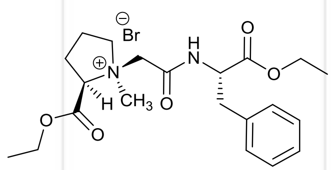

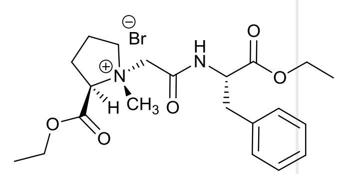

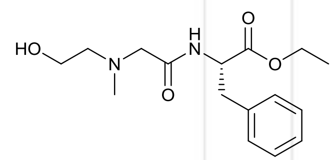

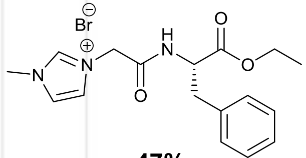

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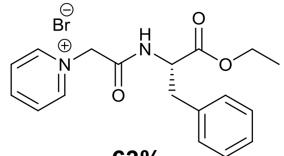

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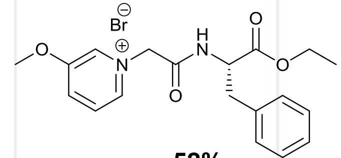

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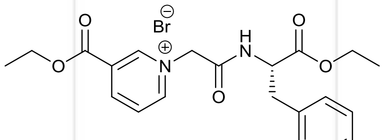

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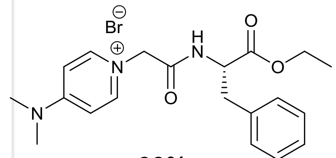

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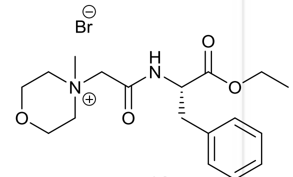

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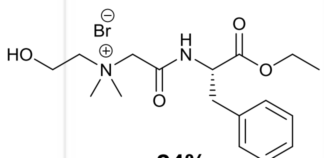

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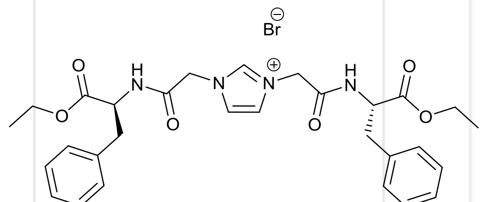

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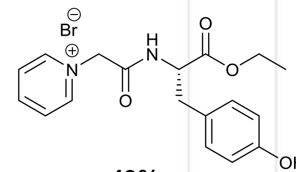

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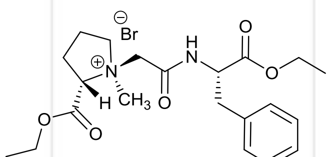

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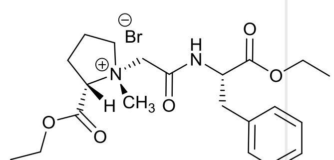

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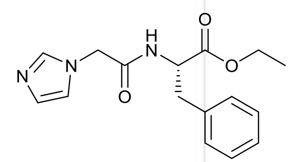

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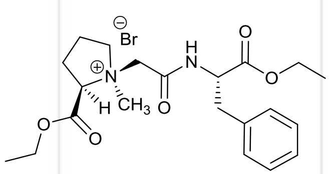

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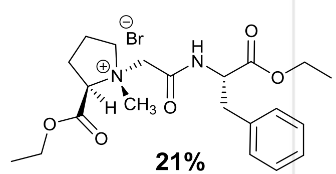

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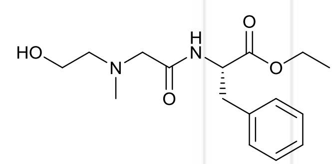

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Synthesis of a series of amino acid derived ionic liquids and tertiary amines: green chemistry metrics including microbial toxicity and preliminary biodegradation data analysis.
Gathergood and Kümmerer et al.
Green Chem. **2016,** 18, 4374-4392

On the way to greener ionic liquids: Identification of a fully mineralizable phenylalanine-based ionic Liquid
Gathergood and Kümmerer et al.
Green Chem. **2016,** 18, 4361-4373

Two Bites at the Cherry

Have we failed?

Guidelines to assist design of safer chemicals

Transformation product directed library selection

Transient Transformation product identification

Tandem Approach

- **Catalyst Performance/Atom Economy/Green Toxicology**

Education

Acknowledgements

Stephen Connon, Klaus Kümmerer,
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PhD Illia Kapitanov (senior research scientist)
PhD Vijai Kumar Gupta (senior research scientist)

PhD Yuri Ermolovich (postdoctoral researcher,)
PhD Mohammed Hassan (postdoctoral researcher)
Pille Pata (researcher), Jaan Parve (chemist)

Eva Doyle (PhD student), Estelle Silm (PhD student)
Grete Raba (PhD student), Gabor Zoltan Elek (PhD student)
Dewi Kurnianingsih Arum (PhD student)
Yulia Konik (Visiting PhD student, Sept 2016-Feb 2017)
Oleksandra Mariichak (Visiting PhD student, Jan 2016-Jun 2017)
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Erni Metsal (MSc student), Bo Lui (MSc Student, DCU)
Aizhamal Subanbekova, (Erasmus student July, August, 2016)
Nele Konrad (BSc student), Anastassia Sikerina (BSc student)

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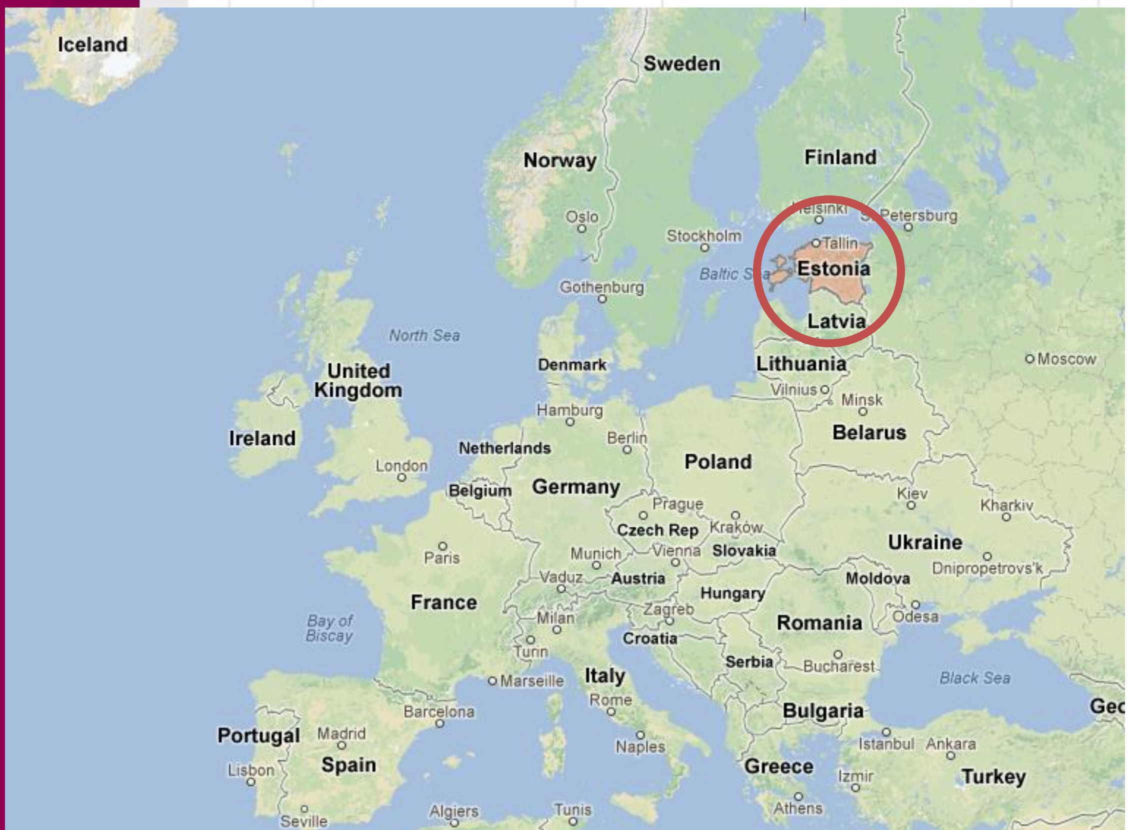
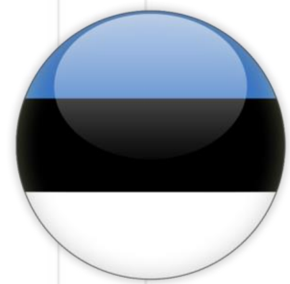


Capital and largest city is **Tallinn**



Tallinn – capital of Estonia

United Nations
Educational, Scientific and
Cultural Organization

World
Heritage
Convention

ERA Chair of Green Chemistry

(Department of Chemistry, Faculty of Science TUT)

This project has received funding from the European Union's 7th Framework Programme for research, technological development and demonstration under grant agreement no 621364

Main research area: *environmentally friendly chemicals and procedures* (biorenewable starting materials, sustainable chemistry, 'benign by design', environmentally friendly procedures and chemicals, catalysis, biodegradation, green toxicology, efficient synthesis, atom economy, green chemistry metrics, asymmetric synthesis, ionic liquids, surfactants, green analytical chemistry (including host-guest interactions), drug discovery (antimicrobials, analgesics, cancer therapeutics) and safer anaerobic adhesives).

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ERA Chair of Green Chemistry

Tallinn University of Technology, Estonia

The concept of Green Chemistry was first introduced in 1998 with the publication of Anastas and Warner's "12 Principles of Green Chemistry". Today, these principles are becoming adopted as general practice in the chemical industries in order to reduce or eliminate the use and generation of hazardous materials, reduce waste, and make use of sustainable resources. New, safer materials and products are being released all the time. Alternative technologies are being developed to improve the efficiency of the chemical industry, while reducing its environmental impact. Sustainable resources are being investigated to replace our reliance on fossil fuels – not only as source of energy but also a source of chemicals — be they feedstock, bulk, or fine. Consideration is now given to the whole life cycle of a product or chemical — from design to disposal. And, as more of the Earth's resources become scarce so new alternatives must be found.

As the world works towards meeting the needs of the present generation without compromising the needs of the future, this series presents comprehensive books from leaders in the field of green and sustainable chemistry. The volumes will offer an excellent source of information for professional researchers in academia and industry, and postgraduate students across the multiple disciplines involved.

Forthcoming titles:

- Functional Materials from Lignin: Methods and Advances
- An In-Depth History of Environmentally Sustainable Energetic Materials
- Toward Added-Value Chemicals by Dehydration of Bio-Based Compounds

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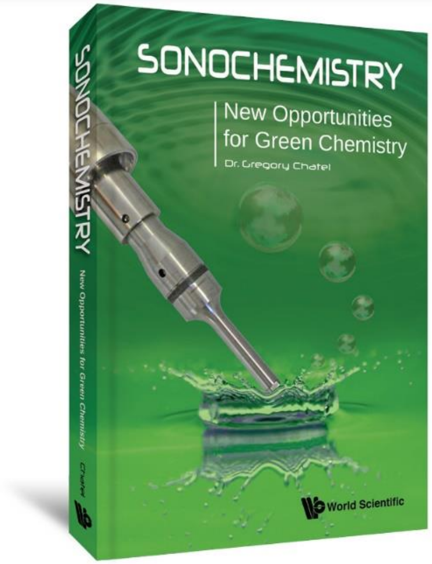


Textbook

Sonochemistry

New Opportunities for Green Chemistry

by **Gregory Chatel** *(Université Savoie Mont Blanc, France)*

This book first introduces the basics of ultrasonic waves and the history of sonochemistry before moving on to look at acoustic cavitation and the estimation of ultrasonic parameters. After this comes a discussion of the equipment needed for experimentation with sonochemistry. Finally there is an in-depth look at green sonochemistry in different fields of research, covering concepts such as new combinations of ultrasound with ionic liquids, microwave irradiation, enzyme combination, and sono-assisted electrochemistry. In conclusion, distinguished sonochemists from around the world share their opinions on the green sonochemistry, and their predictions in the field.

Contents: Introduction; Acoustic Cavitation; Ultrasonic Parameters Estimation; Ultrasonic Equipment; Applications in Green Chemistry; Conclusion and Outlook.

Readership: Undergraduate and graduate students in chemistry, and practitioners of ultrasonic technology.

188pp | **Feb 2017**
978-1-78634-127-3 | **US$80 / £66**
978-1-78634-150-1(pbk) | **US$45 / £37**

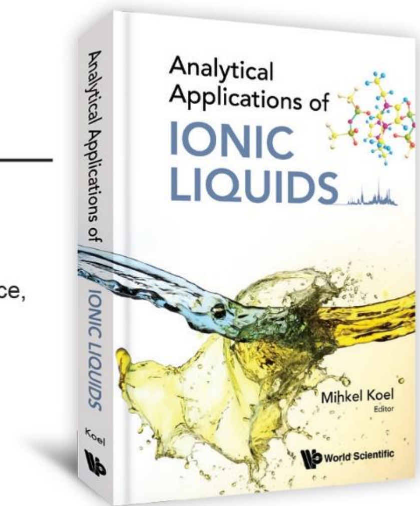
Analytical Applications of Ionic Liquids

edited by **Mihkel Koel** *(Tallinn University of Technology, Estonia)*

This book reviews the current research in analytic chemistry, covering subjects as diverse as separation science, chromatography, spectroscopy and analytical electrochemistry.

Readership: Analytical chemists, undergraduate and graduate students, university professors.

436pp | **Dec 2016**
978-1-78634-071-9 | **US$195 / £162**



DGSC

- The Division of Green and Sustainable Chemistry (DGSC) was approved by EuCheMS in 2015.
- Prof. Pietro Tundo, Chair of the Working Group.
- **Members:** 24, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Poland, Portugal, Spain, Slovakia, Turkey, United Kingdom
- In 2016, the positions of Chair (Nicholas Gathergood, Estonia), Vice-Chair (Piotr Stepnowski , Poland), Secretary (Katalin Barta, Netherlands) and Treasurer (James Sullivan, Ireland) have been elected.
- The Steering Committee of the DGSC was elected in winter 2016 and consists of Nicholas Gathergood, Piotr Stepnowski, Katalin Barta, James Sullivan, Michael North (Next DGSC Conference Chair), José Nuno C Lopes and Ana Aguiar-Ricardo (Past DGSC conference Chairs) and Joel Barault, according to the procedures and practices 3.5(i) of the DGSC.

DGSC Conference Presentation

- EuCheMS Division of Analytical Chemistry supported ECOBALT 2016 conference in Tartu, Estonia in October

- DGSC presentation in DCE conference in Oslo 2017

- DCE presentation in DGSC conference in York 2017

DGSC Activities

Provide expert opinion on green and sustainable chemistry issues

Contribution to a white paper, Biopharma for Europe

DGSC Conferences

- 1st EuCheMS Green and Sustainable Chemistry conference in Budapest in the Autumn of 2013
- 2nd EuCheMS Green and Sustainable Chemistry conference in Lisbon in the Autumn of 2015


EuCheMS
UNIVERSITY of York
3rd EuGSC
3rd EuCheMS
Congress on Green and
Sustainable Chemistry
3-6 September 2017
York, United Kingdom
www.york.ac.uk/3EUGSC

Plenary Speakers

Paul Anastas	Yale University
James Clark	University of York
Ben Feringa	University of Groningen
Nicholas Gathergood	Tallinn University of Technology
Babette Pettersen	Capricorn Venture Partners
Michael Grätzel	EPFL

Save the Date

Early bird registration deadline
28 February 2017

Oral abstract submission deadline
28 February 2017

Poster abstract submission deadline
30 June 2017