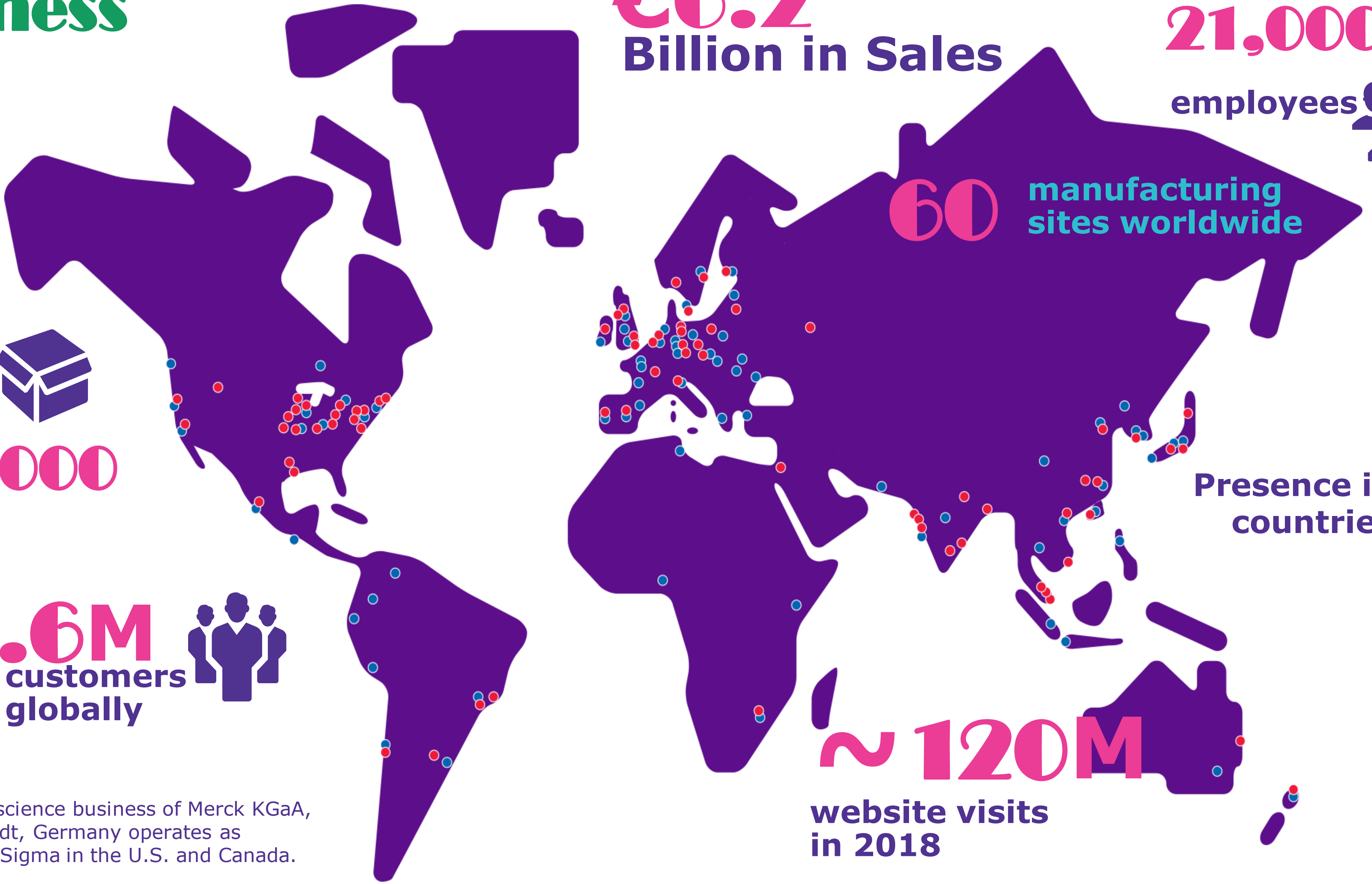
Commercial Introduction of Novel Green solvents to the scientific community

Jane Murray PhD
Global Head of Green Chemistry

Life Science

Business



€6.2
Billion in Sales

21,000
employees

60 manufacturing sites worldwide

Presence in 66 countries

More than
300,000
products

>1.6M
customers globally

~120M
website visits in 2018

The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

Greener Alternative Products

MERCK

Greener Products and Solutions
Re-engineering: 12 Principles of Green Chemistry

Our re-engineering approach is guided by the 12 Principles of Green Chemistry, which help us uncover how to make chemicals, processes or products greener.

12 Principles of Green Chemistry

- #1 Waste Prevention (R)
- #2 Atom Economy (R)
- #3 Less Hazardous Chemical Synthesis
- #4 Designing Safer Chemicals
- #5 Safer Solvents and Auxiliaries
- #6 Design for Energy Efficiency
- #7 Use of Renewable Feedstocks
- #8 Reduce Derivatives
- #9 Catalysis
- #10 Design for Degradation
- #11 Real-time Analysis for Pollution Prevention
- #12 Inherently Safer Chemistry for Accident Prevention

Greener Products and Solutions

Greener Alternatives

Through our **greener alternatives portfolio**, we offer more than **700** greener alternative products—providing customers with important alternatives to reduce their environmental impact.

These products are marked with this icon

TM

DfS Developed Products

12 Principles Aligned Products

Re-engineered Products

Enabling Tech Products

Greener Products and Solutions

Re-engineered Products

We re-engineer products to manufacture with fewer resources, in a less hazardous manner and/or to generate less waste.

These are analyzed using **DOZN™** to identify what makes them greener.

Re-engineered Products

Greener Products and Solutions
Re-engineering: DOZN™

An industry first, **DOZN™** is our proprietary Quantitative Green Chemistry Evaluator that enables us to consistently evaluate different products and processes against the 12 Principles of Green Chemistry—clarifying what's "greener" about our greener alternatives.

To evaluate products and processes using DOZN™, we group the 12 Principles of Green Chemistry into three major categories:

1. **Improved Resource Use**
2. **Increased Energy Efficiency**
3. **Reduced Human and Environmental Hazards**

Then, an aggregate score on a scale of 0-100 is given, with 0 being the most desired.

Greener Products and Solutions
DOZN™ in Action: β-Amylase

β-Amylase—an enzyme commonly found in sweet potatoes—hydrolyzes starch into sugar.

6,000 lbs
of sweet potatoes

2,000 lbs
of sweet potatoes

1,900 gallons
of acetone

No solvent required

Significant use
of electricity

No electricity required

Greener Products and Solutions
DOZN™ in Action: β-Amylase

	12 Principles of Green Chemistry	Percentage of Improvement	Results
Resource Used	Atom Economy	52%	Increased yield. Used less raw materials.
Resource Used	Waste Prevention	55%	Eliminated use of organic solvents. Reduced waste.
Resource Used	Reduce Derivatives	N/A	
Resource Used	Renewable Feedstocks Use	71%	More efficient sweet potato use. Reduced auxiliary chemicals.
Resource Used	Real-Time Pollution Prevention	N/A	
Resource Used	Catalyst	N/A	
	Energy Efficiency Design	100%	Eliminated need for elevated temperature and pressure.
Human & Environmental Hazards Reduction	Less Hazardous Chemical Synthesis	96%	Water-based solutions replaced organic solvents. Removed toxic filtering agents.
Human & Environmental Hazards Reduction	Safer Chemical Design	N/A	
Human & Environmental Hazards Reduction	Safer Solvents and Auxiliaries	100%	Eliminated all organic solvents.
Human & Environmental Hazards Reduction	Design for Degradation	No Change	No increased impact with new procedure.
Human & Environmental Hazards Reduction	Inherently Safer Chemical for Accident Prevention	54%	Eliminated flammability and reactivity dangers.

TOTAL PERCENT IMPROVEMENT 95%

AGGREGATE SCORE
0= Most Desirable

100 — 0
Previous Score: 43
Re-engineered Score: 2

Greener Products and Solutions
Re-engineered Products

Here is a snapshot of several products we re-engineered using **DOZN™**:

Product	Old Score	New Score
1-Aminobenzotriazole	94	22
1,3,5-Tris(4-Iodophenyl)benzene	100	4
(DHQD)2 PHAL	13	3
N-Benzoyl-L-threonine methyl ester	21	4
Tetramethyl tin	15	5
(S)-(-)-3-Chloro-1-phenyl-1-propanol	55	5
5β-Pregnane-3α,20α-diol	83	7
N-Maleoyl-β-alanine	17	6
β-Nicotinamide adenine dinucleotide hydrate	57	1
4-Nitrophenyl β-D-xylopyranoside	100	49

Greener Products and Solutions

Enabling Tech Products

Enabling Tech Products help make greener alternatives possible by supporting alternative energy and fuels research.

Enabling Tech Products

Greener Products and Solutions

Enabling Tech Products

Product Examples:
Enzymes for Alternative Energy Research

- Cellulases
- Hemicellulase and Xylanase
- Pectinase, Pectolyase, and Pectinesterase
- Lignin Related Enzymes

Product Examples:
Alternative Energy Materials

- Energy Generation
  - Materials for organic and inorganic photovoltaics, thermoelectrics
- Energy Storage
  - Materials for battery electrodes and electrolytes, fuel cells, ultracapacitors
- Energy Efficiency
  - Materials for lighting – phosphors, OLEDs

Greener Products and Solutions
12 Principles Aligned Products

Cyrene™—a bio-based, dipolar aprotic solvent that is a safer, more sustainable alternative for Dimethylformamide (DMF) and N-Methyl-2-pyrrolidone (NMP)—both of which are under increased regulatory restriction through REACH. Exclusively available from Merck.

This aligns with Green Chemistry Principle #5—**Safer Solvents and Auxiliaries**.

MERCK

Strathclyde University/ GSK Partnership
Solvent Selection Guide

ROYAL SOCIETY OF CHEMISTRY

View PDF Version | Previous Article | Next Article

DOI: 10.1039/C2GC36378J (Communication) *Green Chem.*, 2012, **14**, 3016-3019

Show Compounds | Show Chemical Terms

Replacement of dichloromethane within chromatographic purification : a guide to alternative solvents†‡

Donna S. MacMillan [a], Jane Murray [b], Helen F. Sneddon [c], Craig Jamieson [a] and Allan J. B. Watson *[a]

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Strathclyde University/ GSK Partnership
Solvent Selection Guides

Green Chemistry — RSC Publishing

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Cite this: *Green Chem.*, 2013, **15**, 596

Received 27th November 2012, Accepted 19th December 2012

DOI: 10.1039/c2gc36900a

www.rsc.org/greenchem

Evaluation of alternative solvents in common amide coupling reactions: replacement of dichloromethane and *N*,*N*-dimethylformamide†

Donna S. MacMillan,[a] Jane Murray,[b] Helen F. Sneddon,[c] Craig Jamieson[a] and Allan J. B. Watson*[a]

Green Chemistry — RSC Publishing

COMMUNICATION — View Article Online | View Journal | View Issue

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www.rsc.org/greenchem

Development of a solvent selection guide for aldehyde-based direct reductive amination processes†

Fiona I. McGonagle,[a] Donna S. MacMillan,[a] Jane Murray,[b] Helen F. Sneddon,[c] Craig Jamieson[a] and Allan J. B. Watson*[a]

University of Strathclyde Glasgow

gsk

RSC Publications- amongst most downloaded articles

MERCK

PRODUCT HIGHLIGHT

Greener Solvent Alternatives

The 12 Principles of Green Chemistry

The green chemistry concept applies innovative scientific solutions to solve environmental issues. The 12 Principles of Green Chemistry, developed by Paul T. Anastas and John C. Warner, can be grouped into "Reducing Risk" and "Minimizing the Environmental Footprint."

Sigma-Aldrich strives to support the growth of greener technologies and manufacturing. We provide application-based greener solvent alternatives for use in chemical reactions and chromatography—reducing both risk and the environmental footprint.

Principle 5. Safer Solvents and Auxiliaries
The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

Look for the Greener Alternatives Program icon on our website.

Greener Solvents and Their Applications

Prod. No.	Solvent Alternatives	Undesired Solvents	Applications
745588	Ethyl acetate/Ethanol 3:1 (v/v) solution, CHROMASOLV®	DCM	Purification, Analysis[1]
34873	Heptane, CHROMASOLV®, for HPLC, ≥99%	Hexane, pentane	Reaction, Analysis[3]
246654	Heptane, anhydrous, 99%	Hexane, pentane	Reaction, Purification[7]
673277	2-Methyltetrahydrofuran, anhydrous, ≥99%, inhibitor-free (2-MeTHF)	DCM, THF, diisopropyl ether, diethyl ether	Reaction[4]
414247	2-Methyltetrahydrofuran, anhydrous, ≥99.0%, contains 250 ppm BHT as stabilizer (2-MeTHF)	DCM, THF	Reaction[4]
791962	Cyclopentyl methyl ether, anhydrous, ≥99.9%, inhibitor free (CPME)	THF, MTBE, 1,4-dioxane and other ether solvents	Reaction[5] Purification[8]
675970	Cyclopentyl methyl ether, anhydrous, ≥99.9%, contains 50 ppm BHT as inhibitor (CPME)	THF, MTBE, 1,4-dioxane and other ether solvents	Reaction[5] Purification[8]
270989	Ethyl acetate, anhydrous, 99.8%	DCM, DCE	Reaction, Purification[7]
517127	Dimethyl carbonate, anhydrous, ≥99% (DMC)	DMF, DCM, DME	Reaction[8]
244511	Toluene, anhydrous, 99.8%	Benzene	Reaction[7]
271004	Acetonitrile, anhydrous, 99.8%	DMF, DMA, NMP	Reaction[7]

For more information, visit **sigma-aldrich.com/green**

References:
[1] A convenient guide to help select replacement solvents for dichloromethane in chromatography. Taygerly, J. P. et al. Green Chem. 2012, 14, 3020.
[2] Sustainable Practices in Medicinal Chemistry: Current State and Future Directions. Alfonsi, K. et al. J. Med. Chem. 2013, 56, 6007.
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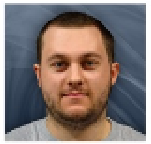
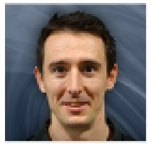
[4] 2-Methyltetrahydrofuran (2-MeTHF): A Biomass-Derived Solvent with Broad Application in Organic Chemistry. Pace, V. et al. ChemSusChem 2012, 5, 1369.
[5] The toxicological assessment of cyclopentyl methyl ether (CPME) as a green solvent. Watanabe, K. Molecules 2013, 18, 3183.
[6] Replacement of dichloromethane within chromatographic purification: a guide to alternative solvents. MacMillan, D. S. et al. Green Chem. 2012, 14, 3016.
[7] Expanding GSK's solvent selection guide – embedding sustainability into solvent selection starting at medicinal chemistry. Henderson, R. K. et al. Green Chem. 2011, 13, 854.
[8] Evaluation of alternative solvents in common amide coupling reactions: replacement of dichloromethane and N,N-dimethylformamide. MacMillan, D. S. et al. Green Chem. 2013, 15, 596.

Development of Solvent Selection Guides


Mr. H. E. Eastman


Prof. C. Jamieson


Prof. A. J. B. Watson

Harry E. Eastman, Craig Jamieson, and Allan J. B. Watson*

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Keywords. environment; green chemistry; sustainability; solvents; selection guides.

Abstract. A review of the development of solvent selection guides that focuses on the efforts of major pharmaceutical companies and several academic groups to provide guides that facilitate the selection of more benign solvents for use in synthetic chemistry.

Outline

1. Introduction
2. Development of Solvent Selection Guides
   2.1. General Solvent Selection Guides
   2.2. Task-Specific Solvent Selection Guides
      2.2.1. Chromatography
      2.2.2. Reaction-Specific Solvent Selection Guides
3. Conclusions and Outlook
4. Acknowledgments
5. References

1. Introduction

The sustainability of chemical processes is of increasing importance within the chemical industry and is becoming a key concern for a wider range of practitioners.[1] Historically, process chemists have been the leading proponents of sustainable chemistry practices and, while this does remain integral to chemical development operations, sustainability is now becoming a significant consideration earlier on in the discovery phase of industrial, as well as academic, research.[2]

In this regard, solvent is one of the largest overall components used in chemical reactions. For example, solvent has been estimated to account for over half of the total material utilized to manufacture active pharmaceutical ingredients.[3] Based on this knowledge, and perhaps unsurprisingly, solvent was identified very early on in the sustainable chemistry revolution as a priority area for research because of the direct and substantial impact that a change in this area may have.

Consequently, over approximately the past 15 years, efforts have been made to identify existing solvents that exhibit undesirable properties from an environment, health, and safety (EHS) perspective such that, wherever possible, solvents with an unacceptable profile may be avoided. In addition, considerable research has been invested in identifying replacements for solvents that are less favorable from a sustainability perspective. These efforts have resulted in a series of solvent selection guides that helpfully describe the alignment of a broad range of widely used solvents with sustainable chemistry principles.

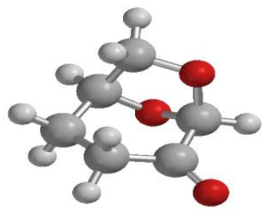
2. Development of Solvent Selection Guides

Two principal approaches have been taken toward providing guidelines to assist with solvent selection. The first helps the practitioner select a priori a more sustainable solvent for a reaction, while the second approach allows an existing less favorable solvent to be supplanted with a more benign alternative. A series of reports have emerged over the past 15 years from leading pharmaceutical companies detailing their assessment of what solvents they consider to be favorable or unfavorable (and anywhere in between). Their evaluations were based on a range of criteria encompassing EHS considerations and considerations that relate to operational costs and impact on life-cycle management.[4–8] In a more applied approach, several industrial and academic groups have published task-specific guides to help facilitate the replacement of an unfavorable solvent within widely used processes or reactions such as chromatographic purification,[9,10] amide-bond formation,[11] reductive amination,[12] and olefin metathesis.[13]

2.1. General Solvent Selection Guides

As stated above, the development of solvent selection guides has been driven principally by industry, in particular, by several large pharmaceutical companies.[4–8] Accordingly, the guidance delivered is broadly similar, with typically only small variations in the perceived environmental impact of a particular solvent, and these variations are generally related to the nature and number of the variables being

Scope and Limitations of Cyrene



Scope and limitations of a DMF bio-alternative within Sonogashira cross-coupling and Cacchi-type annulation

Kirsty L. Wilson, Alan R. Kennedy, Jane Murray, Ben Greatrex, Craig Jamieson and Allan J. B. Watson*

Beilstein J. Org. Chem. 2016, 12, 2005–2011.
doi:10.3762/bjoc.12.187

In summary, we have developed a mild and robust method for the Sonogashira reaction, employing the bio-derived and sustainable alternative to DMF, Cyrene. In addition, we have shown the capacity for extension of the utility of this new solvent towards enabling the cascade synthesis of functionalised indoles and benzofurans via a Cacchi-type annulation. ***Perhaps more importantly, we have documented some of the limitations of the use of Cyrene as a solvent, providing guidance emerging in relation to the thermal and chemical (base) stabilities of this promising green solvent.***

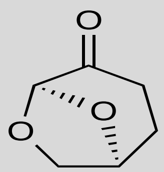
Common Medicinal Chemistry & Agrochemical Reactions

reaction type	no. of reactions	% of total	% of subtype
heteroatom alkylation and arylation	1687	23.1	
N-substitution with alkyl-X	390		23.1
reductive amination	386		22.9
N-arylation with Ar-X	458		27.1
amide N-alkylation	49		2.9
aniline N-alkylation	1		0.05
heteroaryl N-alkylation	44		2.6
O-substitution	319		18.9
S-substitution	30		1.8
acylation and related processes	1635	22.4	
N-acylaton to amide	1165		71.3
N-sulfonylation	163		9.9
N-acylation to urea	155		9.5
carbamate/carbonate formation	42		2.6
amidine formation	4		0.2
O-acylation to ester	13		0.8
O-sulfonylation	75		4.6
other	18		1.1
C—C bond formation	841	11.5	
Suzuki coupling	338		40.2
Heck reaction	3		0.4
Sonogashira reaction	155		18.4
Stille reaction	17		2.0
other Pd-catalyzed reactions (Negishi, Kumada, etc.)	11		1.3
ester condensation	46		5.5
Grignard	47		5.6

For reviews, see: (a) S. D. Roughley, A.M.Jordan, *J. Med. Chem.*, **2011**, 54, 3451-3479.

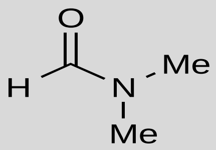
MERCK

Cyrene as a DMF alternative in Cross-Couplings



Cyrene

- B. Pt.: 203 °C
- Density: 1.25 g/mL
- Dipolarity (p*): 0.93

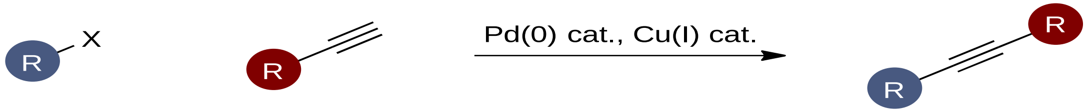


DMF

- B. Pt.: 153 °C
- Density: 0.94 g/mL
- Dipolarity (p*): 0.88

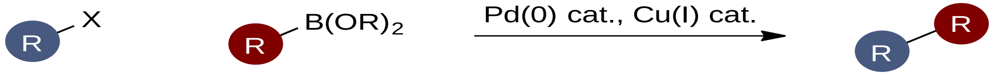
- Derived from cellulose in two steps
- Highly renewable
- No known safety issues

Sonogashira



aryl iodide **terminal alkyne** **internal alkyne**

Suzuki-Miyaura



aryl iodide **organoboron** **biaryl**

Wilson, K. L.; Kennedy, A. R.; Murray, J.; Greatrex, B.; Jamieson, C.; Watson, A. J. B. *Beilstein J. Org. Chem.* **2016**, *12*, 2005.
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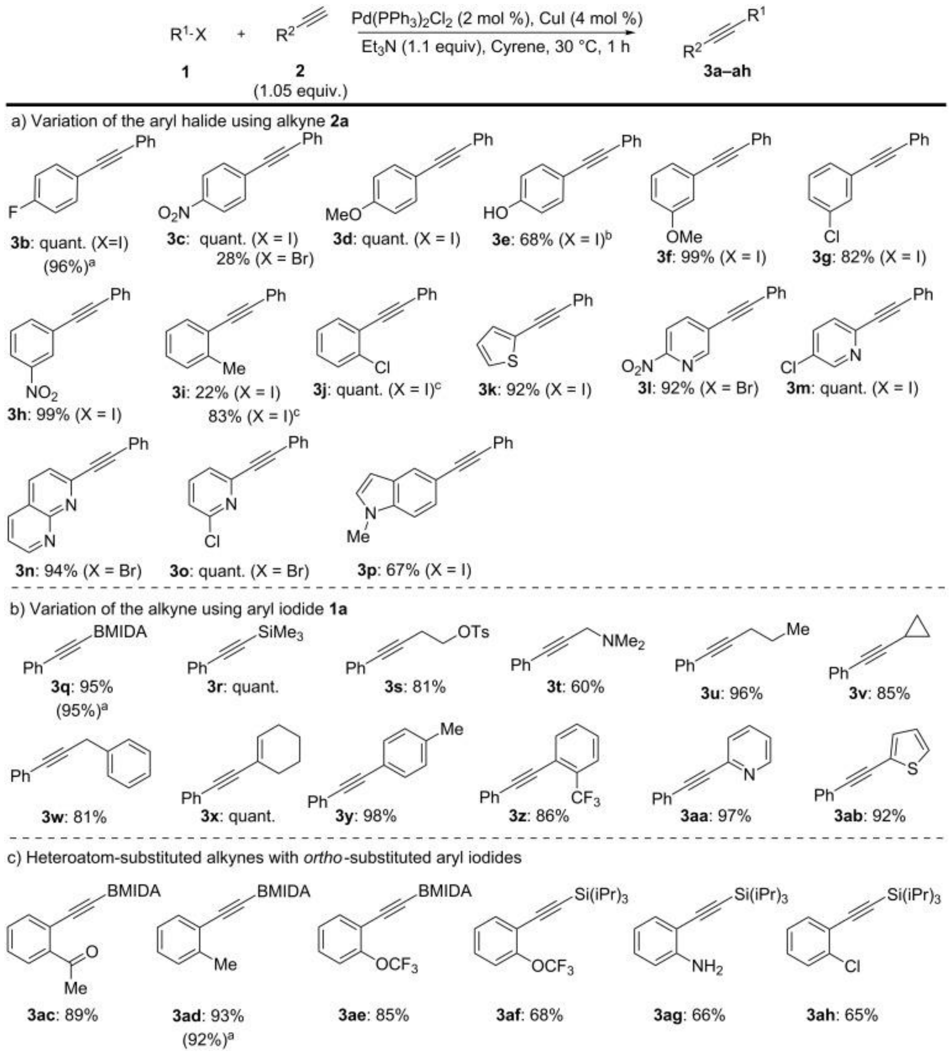
Cyrene as a DMF Alterntaive in Sonogashira Cross-Couplings



- Cyrene compared very favourably with DMF and THF
- Range of aryl and hetroaryl halides tolerated, inc electron deficient aryl bromides
- Functionality on alkyne tolerated
- *Ortho*-amino *and ortho*-hydroxyaryl iodides affords indole, benzofuran and aza-indole scaffolds in single operation

Wilson, K. L.; Kennedy, A. R.; Murray, J.; Greatrex, B.; Jamieson, C.; Watson, A. J. B. *Beilstein J. Org. Chem.* **2016**, *12*, 2005.
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Greener Products and Solutions
Customer Scorecard

You don't know what all you use until you do.

Environmental Opportunity Dashboards

Highlighting:

- Potential Solvent Switches
- Packaging Improvements
- Polysytrene Cooler Return Program
- Carbon Footprint Reduction Opportunities

We're starting the conversation on Green Chemistry in labs around the world.

[redacted] + MilliporeSigma

Environmental opportunity Dashboard

MilliporeSigma reviewed purchases for the last five quarters and found a number of ways to help [redacted] reach its sustainability goals. The majority of what we found can be split into two categories: Solvent Usage and Packaging Savings. Below are several suggestions to reduce the use of hazardous solvents and to eliminate a significant amount of packaging waste.

Currently Using		Potential Replacement
2-Propanol 856 L		Cyclopentyl methyl ether (CPME)**
Acetone 2,843 L		4-hydroxy-4-methyl-2-pentanone
Acetonitrile 713 L		Dimethyl Sulfoxide
Chloroform 253 L	Ethyl Acetate	2-Me-THF*
Cyclohexane 10 L	2-Me-THF*	Cyclopentyl methyl ether (CPME)**
Dichloromethane 1,106 L	Ethyl Acetate	3:1 Ethyl Acetate/ Ethanol, 2-Me-THF*
Diethyl Ether 548 L	2-Me-THF*	Cyclopentyl methyl ether (CPME)**
Dimethylformamide 43 L		Cyrene***, Dimethyl Sulfoxide
Dimethylsulfoxide 58 L		Cyrene :Ionic liquids
Ethyl Acetate 843 L	2-Me-THF*	Cyclopentyl methyl ether (CPME)**
Ethyl alcohol 491 L		2-Propanol
Heptane 24 L		Cyclopentyl methyl ether (CPME)**
Hexane 1,146 L		Cyclopentyl methyl ether (CPME)**
Methanol 556 L		2-Propanol, Ethyl Alcohol
n-Pentane 43 L		Cyclopentyl methyl ether (CPME)**
Tetrahydrofuran 111 L		2-Me-THF*
Toluene 147 L		n-Propylpropionate
Xylene 49 L		Methyl Amyl Ketone, n-Propylpropionate, Isobutyl isobutyrate

Least Desirable — More Desirable

Based on GlaxoSmithKline's Solvent Selection Guide

*2-Me-THF: Alternative to organometallic reactions (Grignard, lithiation, hydride, reduction, metal-catalyzed coupling reactions) solvent and replacement to Dichloromethane in alkylation, amination, and nucleophilic substitutions reactions (Ref: Organic Process Research & Development 2007, 11, 156-159)

**CPME: Replacement for diethyl ether, THF and 1,4-dioxane for reactions, extractions, and crystallizations solvents with high recovery rates (>90%). It has improved yields in Pinner reactions and also it is stable in both acidic and basic conditions. (Ref: Organic Process Research & Development 2007, 11, 251 and Synth. commun. 2009, 39, 2008)

***Available later in 2016

These are based off general trends. Application specific recommendations available upon request.

Greener Products and Solutions

Education Advocacy

Generations of Change

Why Change What Works?

- Resource Constraint
- Environmental Challenges
- Changing Customer Tastes and Buying Habits

Green Chemistry Education Partnership

MERCK + beyondbenign green chemistry education

my green lab.

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Questions?

Greener Products and Solutions

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