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## Accepted Article

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**Authors:** James Sherwood

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# The European 1,2-Dichloroethane Ban Should Liberate not Limit C-H Activation Research and Development

James Sherwood<sup>[\*]</sup>

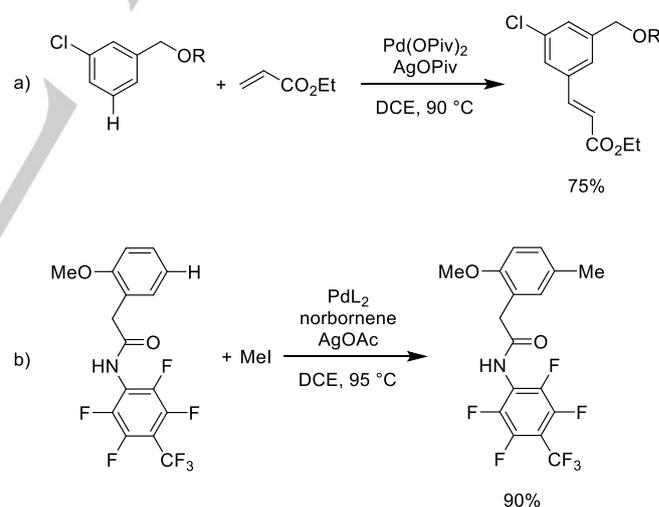
The popular solvent 1,2-dichloroethane (DCE, also known as ethylene dichloride) was recently subject to regulatory controls in the European Union that will severely limit its commercial use. The 'Registration, Evaluation, Authorisation and restriction of CHemicals' (REACH) legislation was created to protect people and the environment from hazardous chemicals.<sup>[1]</sup> Enforced as European law in 2007, the influence of REACH had gradually widened over time. As a known carcinogen, DCE first fell under scrutiny as a 'substance of very high concern' (SVHC) in 2011. From 22th November 2017, REACH now requires companies to gain authorisation before they can use DCE, in any quantity.<sup>[2]</sup> At the present time 8 authorisations have been granted from 20 applications.<sup>[3]</sup> The remaining applications are still being evaluated, while the deadline for submitting new applications has now passed. The total cost of authorisation varies, but an average of €230,000 is often quoted (amassing consultancy, legal and technical costs on top of the application fee).<sup>[4]</sup> Consequently, countless uses of DCE must have been modified to operate with a different solvent, or just discontinued. Those authorisations that have been granted permit the continued use of DCE for between 4 and 12 years. Once that time has elapsed an extension must be applied for, but the hope is that these processes would have been improved by then to eliminate any need for DCE.

New chemical methods being developed within the European Union (EU) that utilise DCE as a solvent or reagent are now constrained to the labs of universities and small non-commercial R&D facilities. The regulatory controls applied to DCE under REACH do not apply to its use in scientific research if carried out in volumes of less than one tonne a year (as stated in REACH article 3-23 and article 56-3).<sup>[1]</sup> One tonne of DCE is slightly less than 800 litres given its high density. Although REACH makes an adequate allowance for R&D activities, there is no permissible quantity allowed in EU manufacturing or formulating processes unless the company has the necessary authorisation. This should be a clear message to researchers that if DCE is integral to their work, opportunities for commercialisation and impact outside of academic publications will be severely limited.

It is not only EU scientists who should be proactive in looking for a replacement for DCE and other SVHC designated chemicals. Regions outside Europe are updating their own legislation controlling the use of toxic chemicals. In the near future these regulatory controls will follow the lead of REACH and prevent the routine use of highly hazardous substances. Several Asian countries are implementing their own REACH-style regulations,<sup>[5]</sup> and the USA has recently revamped its Toxic Substances Control Act (TSCA). The 2016 amendment of TSCA

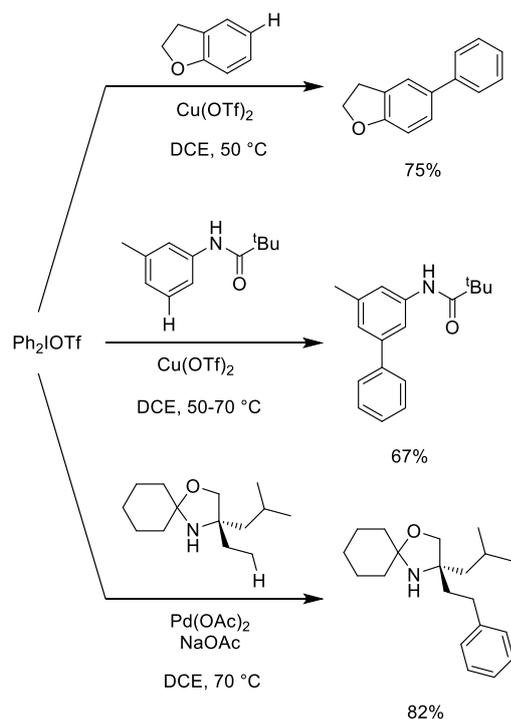
requires that priority chemicals are subject to risk evaluations to decide appropriate control measures.<sup>[6]</sup> Of the first ten chemicals to be evaluated, seven have solvent applications (including dichloromethane and trichloroethylene). With time, equivalent processes to those begun under REACH will be in force under TSCA, prohibiting the manufacture, import, and use of chlorinated solvents (for example) in specified applications. The widening scope of international chemical regulations means DCE is likely to be subject to more restrictions across the world in the coming decade.

One of the chemistries that will be most hurt by the REACH authorisation requirement for DCE is the activation of carbon-hydrogen bonds. This synthetic discipline has flourished in recent years, with high-profile research revealing many new and valuable methods.<sup>[7]</sup> The prospect of being able to selectively modify unfunctionalised hydrocarbons, in a controlled manner, has understandably caused much excitement. However, a common theme connecting different examples of C-H bond activation is the frequent use of DCE as a solvent. This is certainly a barrier that will limit future developments. Prominent examples of C-H bond activation where DCE is needed are provided in Scheme 1 and Scheme 2.<sup>[8-10]</sup>



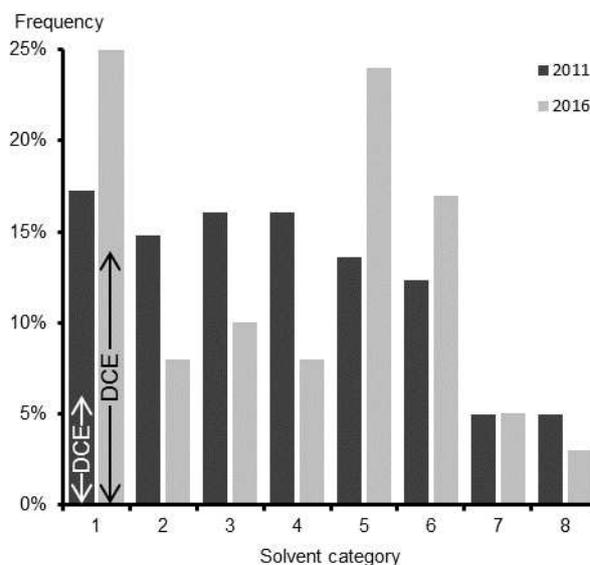
**Scheme 1.** Examples of chemistry performed in DCE. a) Alkyne arylation (R = 4,6-di-tert-butyl-2-(4'-isobutyl-2'-methylpentanenitrile-4'-yl)phenyl, OPiv = pivalate).<sup>[8]</sup> b) Selective *para*-directed methylation (L = 2,3,4,6,7,8-hexahydro-5-methoxycyclopenta[b]pyrro[3,2-e]pyridine).<sup>[9]</sup>

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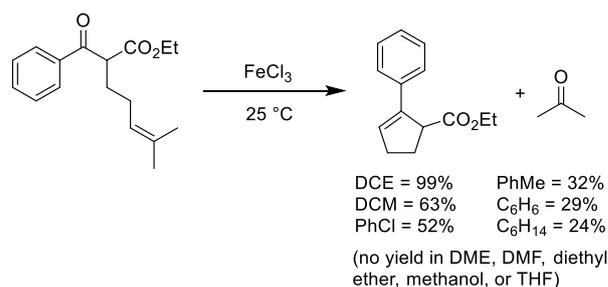
**Scheme 2.** Applications of *bis*(phenyl)iodonium triflate in C-H activation chemistry.<sup>[10]</sup>

With the notable exception of methane functionalisation in the gas phase, C-H bond activation methods are overwhelmingly solution-based and require a solvent. Frank Glorius and co-workers have reviewed the progress made towards establishing mild conditions for C-H bond activation in 2011,<sup>[11]</sup> and again in 2016.<sup>[12]</sup> This permits an insight into evolving solvent use in what could one day be scalable and commercially relevant chemistry. Tallying the solvents indicated in the schemes within those review articles, DCE accounted for 6% of solvents in 2011 (the 5th most common) but became the most popular choice by 2016 at 14% (Figure 1). Overall chlorinated solvent use rose to 25% of examples in 2016, more than any other category of solvent. This is counter to the general trend in industry to reduce chlorinated solvent use. This is not a comprehensive study by any means, but it does provide an indication that the minds of academic and industrial chemists are not aligned when it comes to choosing appropriate solvents, thereby hampering the transition of chemistry from bench to (pilot) plant.



**Figure 1.** Solvent use survey for C-H activation chemistries.<sup>[11-12]</sup> Key: (1) chlorinated solvents; (2) polar aprotics; (3) hydrocarbons; (4) acetic acid and trifluoroacetic acid; (5) alcohols, including fluoroalcohols; (6) ethers; (7) ketones and esters; (8) water. The contribution of DCE to the frequency of chlorinated solvent use is annotated on the chart.

There are many more types of chemistry requiring DCE as a reaction solvent besides C-H bond activation. For instance, a useful technique for converting carbohydrates into a versatile intermediate, 5-(chloromethyl)furfural, has been optimised in a biphasic DCE-hydrochloric acid system.<sup>[13]</sup> Additionally, an iron catalysed intramolecular ring closing metathesis reaction occurs at room temperature to produce cyclopentenones with high yield (Scheme 3).<sup>[14]</sup> A solvent screening saw unrivalled productivity in DCE (99% yield), although modest yields could be obtained in other chlorinated solvents.



**Scheme 3.** A carbonyl-olefin metathesis optimised with a solvent screen.<sup>[14]</sup>

The examples of chemistry provided here are characteristic of how reactions are normally optimised. Often the choice of solvent is made early in the development of the procedure, and once other aspects of the reaction are optimised in that solvent, a late stage substitution rarely provides an improvement to yields. If techniques for the tandem optimisation

of reaction variables were used more widely (e.g. the systematic design of experiments or statistical approaches such as principle component analysis) chemists would understand the role of the solvent with more certainty, and then be in a position to develop synthetic methods that excel in non-toxic, safer solvents.

Nevertheless, DCE possesses properties inherently suited to C-H bond activation and other examples of contemporary chemistry.<sup>[15-17]</sup> It is a chlorinated solvent with a boiling point of 83 °C, making it more suitable than dichloromethane (DCM) or chloroform for the high temperatures that are sometimes required for C-H bond activation (Table 1). 1,2-Dichloroethane is not a Lewis base and is usually considered to be poorly coordinating, although exceptional circumstances to the contrary have been reported.<sup>[18]</sup> The high polarisability of DCE lends itself to the stabilisation of partially formed covalent bonds created as reactions proceed through a transition state. The solvent itself cannot weaken an ordinary C-H covalent bond, but it can enhance the reactivity of catalytic species and stabilise activated complexes. The lack of specific interactions (e.g. hydrogen bonding) yet a strong solvating ability appears to make DCE well suited to C-H bond activation chemistry.

**Table 1.** Properties of DCE, DCM, chloroform and trichloroethylene (TCE).

Property	DCE	DCM	CHCl <sub>3</sub>	TCE
Melting point <sup>[a]</sup> [°C]	-36	-95	-64	-86
Boiling point <sup>[a]</sup> [°C]	83	40	61	87
Vapour pressure at 21 °C <sup>[b]</sup> [mmHg]	71	376	169	56.5
Specific gravity <sup>[b]</sup>	1.253	1.326	1.480	1.464
Viscosity at 25 °C <sup>[b]</sup> [cP]	0.9	0.44	0.57	0.57
Relative permittivity at 25 °C <sup>[a]</sup>	10.36	8.93	4.89	3.42 (16 °C)
Dipole moment <sup>[a]</sup> [10 <sup>-30</sup> .Cm]	6.1	3.8	3.8	2.7
Solubility of water at 25 °C <sup>[b]</sup> [w/w]	0.15	0.20	0.07	0.033
α <sup>[c]</sup>	0.00	0.13	0.20	0.00
β <sup>[c]</sup>	0.10	0.10	0.10	0.05
π* <sup>[c]</sup>	0.81	0.82	0.58	0.53
δ <sub>D</sub> <sup>[d]</sup> [MPa <sup>0.5</sup> ]	18.0	17.0	17.8	18.0
δ <sub>P</sub> <sup>[d]</sup> [MPa <sup>0.5</sup> ]	7.4	7.3	3.1	3.1

δ <sub>H</sub> <sup>[d]</sup> [MPa <sup>0.5</sup> ]	4.1	7.1	5.7	5.3
Flash point <sup>[b]</sup> [°C]	13	None	None	32
Electric conductivity <sup>[b]</sup> [siemen/cm]	4x10 <sup>-11</sup>	4.3x10 <sup>-11</sup>	<10 <sup>-10</sup>	8x10 <sup>-12</sup>
Carcinogenicity <sup>[e]</sup>	H350 May cause cancer	H351 Suspected of causing cancer	H351 Suspected of causing cancer	H350 May cause cancer

[a] Ref. [15]. [b] Ref. [16]. [c] Ref. [17]. [d] HSPIP, 5<sup>th</sup> edition, 2008. [e] Obtained from safety datasheets (Sigma-Aldrich).

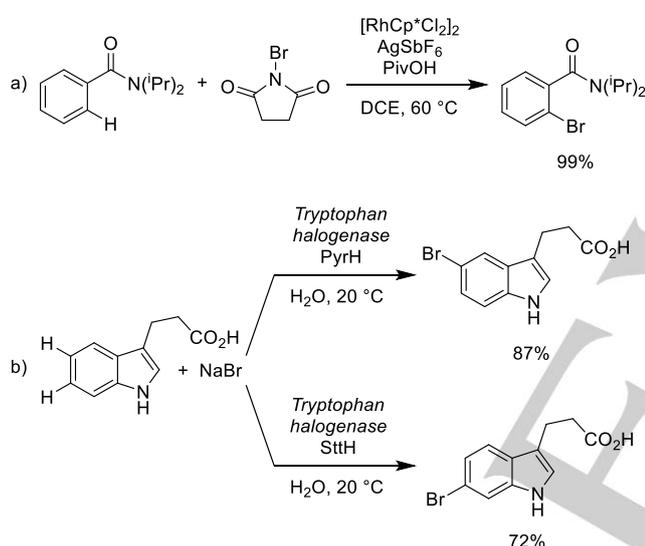
Despite its advantages DCE is flawed in a number of ways. Firstly, DCE may cause cancer and is toxic if inhaled, this being the reason unauthorised uses have been banned in the EU. Furthermore, DCE will react with radicals and can decompose under certain conditions to liberate HCl. This is evidenced by reports of chlorinated by-products found in reactions conducted in DCE.<sup>[14,19]</sup> There is a danger that legislation will push solvent users to replace regulated solvents with obvious, structurally related alternatives. However in the case of DCE, similar solvents such as 1,2-dichloropropane and trichloroethylene are already under legislative scrutiny for the same reasons. Unless a serious attempt to replace chlorinated solvents is made, many emerging chemistries will be prevented from being scaled-up and commercialised. It would be extremely disappointing if the fantastic progress in selective C-H bond activation (and other new reactions reliant on DCE) could never be used to make medicines, specialty surfactants, functionalised polymers, and other types of fine chemical products.<sup>[3]</sup>

The replacement of chlorinated solvents with oxygenated solvents or hydrocarbons is not trivial. Firstly, although the bulk fluid properties of chlorinated solvents (Table 1) are not remarkable individually, the combination is unique: they are volatile yet interact strongly with solutes; immiscible yet more dense than water. The closest approximations to the polarity of chlorinated solvents are provided by aromatic esters and ketones (according to the Hansen solubility parameters δ<sub>D</sub>, δ<sub>P</sub>, and δ<sub>H</sub>). The Kamlet-Taft solvatochromic parameters (α, β, π\*) point to toluene or nitrobenzene. These replacement organic solvents can eliminate some hazards (chronic toxicity, electrical resistivity) but introduce different health hazards and new safety issues, notably increased flammability. Some undesirable physical properties will also need to be dealt with (e.g. higher boiling points, greater water solubility). Ultimately it is the molecular properties of DCE and other chlorinated solvents rather than their macroscopic (bulk) properties that differentiates them,<sup>[20,21]</sup> and so there are no quick fixes.

To successfully implement non-halogenated solvents some consideration of the reaction conditions is needed. Recently it has been found that tetrahydrofuran,<sup>[22]</sup> acetonitrile,<sup>[23]</sup>

and  $\gamma$ -valerolactone (GVL),<sup>[24]</sup> are effective solvents for C-H bond activation chemistry in the right circumstances. In the latter example, an electrochemical C-H activation rather than a conventional thermal reaction with a chemical oxidant may have contributed to better yields of 2-(2-morpholinobenzamido)pyridine-1-oxide in GVL (65%) compared to DCE (11%).

The development of enzymatic transformations is another welcome advance that promises to improve the efficiency and safety of C-H bond activation chemistry.<sup>[25]</sup> Biocatalytic reactions are compatible with water as a solvent, allowing high regioselectivity under mild conditions but without toxic solvents or other hazardous auxiliaries. Enzymatic C-H activation can be used for the halogenation of arenes.<sup>[26]</sup> Although equivalent chemocatalytic procedures can be higher yielding,<sup>[27]</sup> the reaction selectivity is tuneable and achieved under milder conditions (Scheme 4).

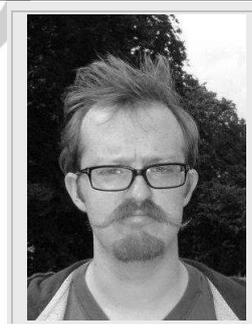


**Scheme 4.** A comparison between methods of introducing bromine into arenes using C-H activation chemistry. a) Chemocatalytic bromination.<sup>[27]</sup> b) Enzymatic bromination with two related biocatalysts for different regioselectivity: tryptophan 5-halogenase PyrH and tryptophan 6-halogenase SttH.<sup>[26]</sup>

The regulatory controls affecting DCE are not a one-off. Inevitably more and more traditionally useful chemicals will be banned, and it is down to chemists to put a positive spin on the current cycle of chemical safety governance and use it to motivate innovation. The chemist that does not look beyond the contents of their round bottom flask will become increasingly irrelevant. Today a holistic perspective of science policy and regulatory trends is needed to design chemistry that is valuable as well as safe and scalable. If the reactions and products we create are to be commercially relevant they must be environmentally benign and have limited toxicity. Contemporary chemistry must be accompanied by a contemporary world view, sharing the positive outlook of the United Nations Sustainable

Development Goals.<sup>[28]</sup> Advocating the use of carcinogenic substances, including DCE, is clearly at odds with sustainable chemistry objectives. Circular economy ambitions led at a political level by Europe,<sup>[29]</sup> and China,<sup>[30]</sup> also need new chemistry to achieve broad interdisciplinary goals. With the unauthorised use of DCE now banned in Europe, and its use in other territories likely to be subject to restrictions in the near future, hopefully the development of C-H bond activation reactions will begin to steer away from chlorinated solvents,<sup>[31]</sup> embracing benign solvents to realise the full potential of this research.<sup>[22-25,26]</sup>

James Sherwood is responsible for alternative solvents research at the Green Chemistry Centre of Excellence (University of York, UK). His research interests include bio-based products and the understanding of solvent effects in organic synthesis. He was involved in the development of an EU standard defining bio-based solvents, and has previously written about sustainable solvents and the circular economy.



## Acknowledgements

I would like to thank Dr. John Hayler (GSK) who drew my attention to the constraints of solvent use in industry and how this limits the types of chemistry that can realistically be taken from academic studies and translated into commercial processes.

**Keywords:** C-H activation • 1,2-Dichloroethane • REACH • Regulation • Solvents

- [1] European Chemicals Agency, Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), <https://echa.europa.eu/regulations/reach/understanding-reach> (accessed 12th January 2018).
- [2] European Chemicals Agency, list of substances included in Annex XIV of REACH ("Authorisation List"), <https://echa.europa.eu/authorisation-list> (accessed 12th January 2018).
- [3] European Chemicals Agency, adopted opinions and previous consultations on applications for authorisation, <https://echa.europa.eu/applications-for-authorisation-previous-consultations> (accessed 12th January 2018).
- [4] UK Chemicals Stakeholder Forum, what you need to know about REACH authorisation (Version 2, November 2015), [www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/473701/Updated\\_Forum\\_Guidance\\_-\\_What\\_does\\_REACH\\_Authorisation\\_mean\\_for\\_my\\_business\\_.pdf](http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/473701/Updated_Forum_Guidance_-_What_does_REACH_Authorisation_mean_for_my_business_.pdf) (accessed 2nd January 2018).
- [5] European Chemicals Agency newsletter, REACH and CLP impact: Chemicals legislation changing in Asia (issue 3, 2012),

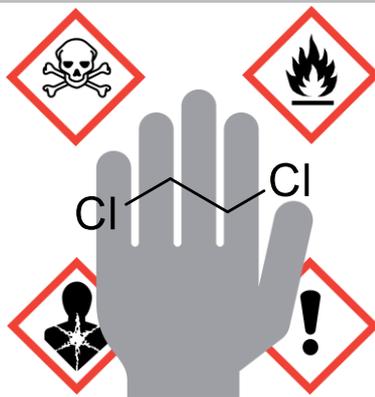
- [https://newsletter.echa.europa.eu/home/-/newsletter/entry/3\\_12-asia](https://newsletter.echa.europa.eu/home/-/newsletter/entry/3_12-asia) (accessed 4th January 2018).
- [6] United States Environmental Protection Agency, risk evaluations for existing chemicals under TSCA, <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluations-existing-chemicals-under-tsca> (accessed 12th January 2018).
- [7] a) C. Feng and T. -P. Loh, *Angew. Chem. Int. Ed.* **2014**, *53*, 2722-2726; *Angew. Chem.* **2014**, *126*, 2760-2764; b) Z. Wang, J. Ni, Y. Kuninobu, M. Kanai, *Angew. Chem. Int. Ed.* **2014**, *53*, 3496-3499; *Angew. Chem.* **2014**, *126*, 3564-3567; c) J. Park, J. Lee, S. Chang, *Angew. Chem. Int. Ed.* **2017**, *56*, 4256-4260; *Angew. Chem.* **2017**, *129*, 4320-4324; d) J. Loup, D. Zell, J. C. A. Oliveira, H. Keil, D. Stalke, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 14197-14201; *Angew. Chem.* **2017**, *129*, 14385-14389; e) P. W. Tan, A. M. Mak, M. B. Sullivan, D. J. Dixon, J. Seayad, *Angew. Chem. Int. Ed.* **2017**, *56*, 16550-16554; *Angew. Chem.* **2017**, *129*, 16777-16781; f) J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62-101; *Angew. Chem.* **2018**, *130*, 64-105.
- [8] D. Leow, G. Li, T. -S. Mei, J. -Q. Yu, *Nature* **2012**, *486*, 518-522.
- [9] X. -C. Wang, W. Gong, L. -Z. Fang, R. -Y. Zhu, S. Li, K. M. Engle, J. -Q. Yu, *Nature* **2015**, *519*, 334-338.
- [10] a) J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer, M. J. Gaunt, *Nat. Chem.* **2015**, *7*, 1009-1016; b) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593-1597; c) C. -L. Ciana, R. J. Phipps, J. R. Brandt, F. -M. Meyer, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2011**, *50*, 458-462; *Angew. Chem.* **2011**, *123*, 478-482.
- [11] J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740-4761.
- [12] T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* **2016**, *45*, 2900-2936.
- [13] M. Mascal, E. B. Nikitin, *Green Chem.* **2010**, *12*, 370-373.
- [14] J. R. Ludwig, P. M. Zimmerman, J. B. Gianino, C. S. Schindler, *Nature* **2016**, *533*, 374-379.
- [15] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry, third edition*, VCH, Weinheim, **2003**.
- [16] I. M. Smallwood, *Handbook of Organic Solvent Properties*, Arnold, London, **1996**.
- [17] Y. Marcus, *Chem. Soc. Rev.* **1993**, *22*, 409-416.
- [18] M. R. Colman, M. D. Noiro, M. M. Miller, O. P. Anderson, S. H. Strauss, *J. Am. Chem. Soc.* **1988**, *110*, 6886-6888.
- [19] G. Qian, X. Hong, B. Liu, H. Mao, B. Xu, *Org. Lett.* **2014**, *16*, 5294-5297.
- [20] G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* **2016**, *116*, 2478-2601.
- [21] E. Stefanis, C. Panayiotou, *Int. J. Pharm.* **2012**, *426*, 29-43.
- [22] Qingqing Bu, Torben Rogge, Vladislav Kotek, Lutz Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 765-768; *Angew. Chem.* **2018**, *130*, 773-776.
- [23] P. Becker, T. Duhamel, C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2018**, *57*, 5166-5170; *Angew. Chem.* **2018**, *130*, 5262-5266.
- [24] Nicolas Sauermann, Ruhuai Mei, and Lutz Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5090-5094; *Angew. Chem.* **2018**, *130*, 5184-5188.
- [25] a); J. Li, X. Tang, T. Awakawa, B. S. Moore, *Angew. Chem. Int. Ed.* **2017**, *56*, 12234-12239; *Angew. Chem.* **2017**, *129*, 12402-12407; b) J. T. Groves, *Nat. Chem.* **2014**, *6*, 89-91.
- [26] J. Latham, J. -M. Henry, H. H. Sharif, B. R. K. Menon, S. A. Shepherd, M. F. Greaney, J. Micklefield, *Nat. Commun.* **2016**, *7*, 11873.
- [27] N. Schröder, J. Wencel-Delord, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 8298-8301.
- [28] D. Griggs, M. Stafford-Smith, O. Gaffney, J. Rockström, M. C. Öhman, P. Shyamsundar, W. Steffen, G. Glaser, N. Kanie, I. Noble, *Nature* **2013**, *495*, 305-307.
- [29] W. R. Stahel, *Nature* **2016**, *531*, 435-438.
- [30] J. A. Mathews, H. Tan, *Nature* **2016**, *531*, 440-442.
- [31] a) M. Bauer, W. Wang, M. M. Lorion, C. Dong, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 203-207; *Angew. Chem.* **2018**, *130*, 209-213; b) M. Nappi, C. He, W. G. Whitehurst, B. G. N. Chappell, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2018**, *57*, 3178-3182; *Angew. Chem.* **2018**, *130*, 3232-3236; c) R. G. Kinney, J. Tjutris, G. M. Torres, N. J. Liu, O. Kulkarni, B. A. Arndtsen, *Nat. Chem.* **2018**, *10*, 193-199; d) C. Yuan, L. Zhu, R. Zeng, Y. Lan, Y. Zhao, *Angew. Chem. Int. Ed.* **2018**, *57*, 1277-1281; *Angew. Chem.* **2018**, *130*, 1291-1295.

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Layout 1:

**ESSAY**

1,2-Dichloroethane was recently subject to regulatory controls in the European Union that will severely limit its commercial use. The practitioners of innovative synthetic methods, particularly C-H bond activation, need to investigate alternative solvents if their chemistry is to stay relevant.

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Layout 2:

**ESSAY**

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Text for Table of Contents