Flow detoxification of a sulfur mustard simulant with organometallic compounds enabled by an optimization algorithm

Valmir Baptista da Silva, Sergui Mansour, Antonin Delaune, François-Xavier Felpin, Julien Legros

Flow detoxification of a sulfur mustard simulant with organometallic compounds enabled by an optimization algorithm†

Valmir Baptista da Silva[a§], Sergui Mansour[a§], Antonin Delaune[a], François-Xavier Felpin*[b] and Julien Legros*[a]

The flow detoxification of the yperite simulant CEES (chloroethyl ethyl sulfide) with PhMgBr or PhLi proceeds in a faster fashion than in a classical batch reactor, to afford the corresponding substitution or dehydrohalogenation product, respectively. An optimization algorithm was deployed to determine the best experimental conditions for full neutralisation with PhMgBr in flow and to allow multigram scaling.

Introduction

Bis(2-chloroethyl) sulfide is notoriously infamous under the common names mustard agent, yperite or HD (Figure 1a). This viscous liquid has been used as a chemical warfare agent (CWA) through dispersion, by spraying or explosion, hence the denomination "mustard gas".‡ The high toxicity of HD stems from its equilibrium with the corresponding episulfonium form, a very strong electrophile (Figure 1a).[1] The disposal of large quantities of mustard agents (such as shells from World War I or Syrian stockpiles) are performed in secured dedicated premises though harsh processes: direct pyrolysis, transformations with aggressive oxidants or hydrolysis in strongly basic solutions. However, the use of water as nucleophilic scavenger for such compounds is deceptively simple since HD, which is insoluble in water, reacts very slowly and undergoes partial oligomerization/hydrolysis, rearranging into micelles that still contain important quantities of unaltered yperite in their core.[2,3] If the insolubility of these harmful molecules can be circumvented by using alcohols as nucleophiles, mustard agents are still reluctant to the direct solvolysis and stronger heteronucleophiles such as alcoholates or amines, eventually combined to high pressures, are required for efficient abatement.[4–8] Among the last decade, numerous efforts have been made to develop innovative and mild methods for this purpose.[9–12] As an alternative, organometallic nucleophiles, such as Grignard reagents, might be a successful strategy for developing mild processes. Whereas this strategy has never been applied for detoxification of CWA purpose, Finn studied the reactivity of various chloroethyl sulfides with organomagnesium reagents for mechanistic studies.[13] Thus, with chloroethyl ethyl sulfide **1** (CEES, the commonly accepted yperite simulant), best results were obtained on a millimole scale with PhMgBr (2.5 equiv.) in toluene/Et_2O at 70 °C for 30 min. to provide **2** in 82% yield (Figure 1b). However, in the context of neutralization of CWA, the development of a process exhibiting high reactions rates and >99% conversions into innocuous compounds while allowing easy scale-up is highly desired. In this context, miniaturised flow reactors have been shown to be exceptional devices that afford chemical reactivities impossible to reach under classical batch conditions.[14–18] Fluidic systems offer the possibility to handle and treat large volumes of hazardous compounds with reduced exposition for the operator.[19] Following the pioneer work of Yoshida,[20–24] highly reactive organometallic species (mostly organolithium compounds[25–30] and then Grignard reagents[31–33]) were shown to be easily tamed in flow microreactors.[34–36] In addition, the fine control brought by miniaturised flow reactors on various parameters (reaction time, temperatures) and the spatial resolution of reaction allowed to get the high selectivities required for the effective detoxification of chemical warfare agents.[37–41] Herein, we now report that the yperite simulant CEES can be efficiently detoxified with organometallic reagents (PhMgBr, PhLi) in a flow system with significant acceleration over usual batch conditions (Figure 1c). An optimization algorithm assisting the decision-making process was used to determine the best neutralisation conditions and to allow application on a multigram scale.

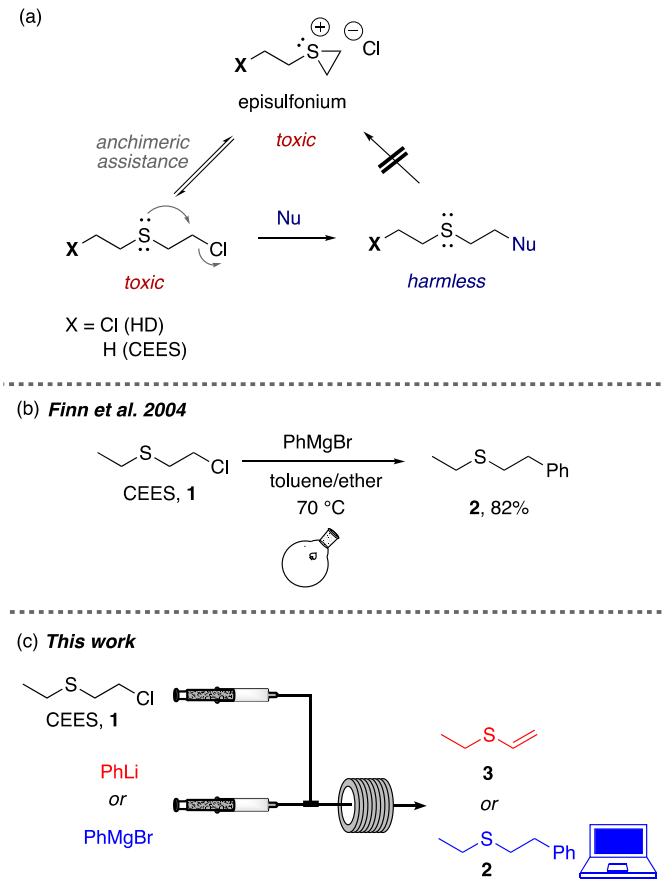

Figure 1. (a) Reactivity of mustard agent HD and its simulant CEES and their neutralization path through nucleophilic substitution. (b) Reactivity of CEES with PhMgBr under batch conditions by Finn et al.[13] (c) Neutralization of CEES with organometallics under flow conditions assisted by an optimization algorithm (this work).

Results and discussion

Organometallic reagents are often stored and commercialized in solutions; the nature of the solvent impacts the aggregation state of such species with important consequences on their reactivity.[42–45] Specifically, Finn showed that aryllithium compounds react with various chloroethyl sulfides to promote elimination in preference to substitution, whereas Grignard reagents give intractable mixtures in ethereal solvents but mostly S_N product in toluene.[13] Thus, in order to compare the reactivity of organometallics for abatement of CEES under batch and flow conditions, PhMgBr (commercialised as solution in Et_2O) and PhLi (commercialised as solution in Bu_2O) were reacted with a solution of CEES in toluene and THF at 20 °C under pseudo-first order conditions. The compared kinetics of CEES disappearance in these two types of reactors are reported in Table 1, providing corresponding rate constants *k* and half-time values ($t_{1/2}$).

Table 1. Kinetics of reaction of CEES with PhLi and PhMgBr under batch and flow conditions.[1]

PhM	k_{obs} (10^{-1} min^{-1})	$t_{1/2}$ (min)	k_{obs} (10^{-1} min^{-1})	$t_{1/2}$ (min)
PhLi	5.0 (± 0.1)	1.4	6.7 (± 0.7)	1.0
PhMgBr	4.4 (± 0.2)	1.6	6.4 (± 0.9)	1.1

[1] Reactions were performed under pseudo-first order conditions with 10 equiv. of the organometallic reagent (with PhLi in Bu_2O/THF and PhMgBr in Et_2O/toluene) and monitored by GC-FID at 20 °C (thermostated bath).

Pleasingly, reaction of CEES took place with both organometallics in batch and in flow conditions. While this is without any consequences on a detoxification perspective, it is worth to note that reaction with PhLi afforded the expected dehydrochlorination product **3**, accompanied with **2** as minor product. With PhMgBr, S_N product **2** was formed along with traces of brominated analogue of CEES (bromoethyl ethyl sulfide, **4**). Whereas brominated analogues of mustard agents find outside the scope of the chemical weapon convention, their toxicity is unknown but their reactivity might be close to that of mustards and they can be thus considered as undesirable. On a kinetic standpoint, we were delighted to observe that reactions were significantly accelerated under flow condition: at least 1.3 times faster than in batch, likely due to better mass transfer in flow microreactors systems that is known to be of importance in such rapid and exothermic reactions.[46]

After having validated the asset of flow chemistry compared to a batch process on reaction kinetics, we focused on the optimization of the detoxification conditions of CEES (>99% conversion/selectivity into innocuous compounds). The dehydrochlorination that occurrs with PhLi affording undesirable volatile compounds (EVS **3** and benzene), the reaction with PhMgBr was chosen for further study. The traditional approach for optimizing chemical reactions consists in defining a set of variables to be modified in order to optimize an objective which is often the yield or the productivity of the considered transformation. To reach this objective it is customary to modify the value of only one variable at a time (OVAT) and to observe the impact of this modification on the defined objective. This approach has the advantage of being very simple to implement but, on the other hand, it does not allow to understand the interactions between variables and can lead to a very large number of experiments to determine a satisfactory optimum, especially for a high dimensional optimization. In order to achieve a more efficient and faster optimization process than the OVAT approach, we used a black box optimization algorithm that works without a priori reaction and gradient information. We recently developed an optimization algorithm based on the Nelder-Mead method that we profoundly modified to improve its efficiency in the context of chemical reaction optimizations.[47]

The major modifications of the Nelder-Mead method that we have implemented include i/ different stopping criteria to limit the number of experiments, ii/ the possibility to temporarily reduce the dimensionality of the search to explore a subspace and iii/ the possibility to diversify or intensify the

exploration of the search space when the algorithm has converged to a local optimum considered as not satisfactory by the operator. The Nelder-Mead method is based on the displacement in the search space of a polytope, also called simplex, of n+1 vertices where n represents the number of variables. Each vertex is represented by a result of the objective and, at each new iteration, the algorithm tries to replace the worst point by a new better point until it converges to an optimum and reaches a stopping criterion.

In this study we aimed to optimize the yield of product **2** obtained by nucleophilic substitution of CEES by PhMgBr. To carry out the optimization we selected the residence time, the number of Grignard reagent equivalent and the temperature as input variables to optimize the yield of product **2** as output variable. A major difficulty associated to this optimization consists in consuming totally the CEES while avoiding the formation of **4**, whose toxicity is certainly close to that of the CEES. Moreover, although it was possible to use black-box optimization algorithms in association with an automated flow reactor,[48–57] we considered that for an optimization of moderate dimensionality (i.e. three variables), the time saved by the contribution of automation would not be critical if the algorithm converged in less than 15 experiments, which is generally what we previously observed with our algorithm on optimizations of equivalent dimensionality. The size of the 3-dimensional search space was defined by the lower and upper bounds of the variables, *i.e.*, in the range of 0.5-30 min, 1-10 equivalents and 0-50 °C, for residence time t^R, PhMgBr equivalents and temperature, respectively. The initial simplex was defined by an initial point X_0 and by its size represented by the d value. We fixed the initial point X_0 at 1 min of residence time, 1 equivalent of PhMgBr and 25 °C with d values of 6 min, 2 equivalents and 10 °C, respectively. Note that d values represent *ca*. 20% of the range of the considered variable as we previously determined that it corresponds to the best compromise between speed of the search (large simplex) and quality of the optimum (small simplex).

After performing the experiments corresponding to the initial simplex and communicating the results to the algorithm, the optimization started (Figure 2). After each experiment, analyzed by off-line GC to determine the proportions of the starting CEES and the products formed, the algorithm suggested a new set of experimental conditions and this iterative process was continued until convergence. While the desired product yield did not exceed 69% in the initial simplex, the algorithm provided a spectacular improvement in the 5th experiment, leading to a GC yield for **2** of *ca*. 90%. Only 5 additional experiments were required to obtain **2** with >99% yield which was a stopping criterion for the algorithm. This study shows the usefulness and the power of an optimization algorithm to converge in only 10 experiments towards the initial objective: >99% yield in target product **2** and total disappearance of CEES and **4**.

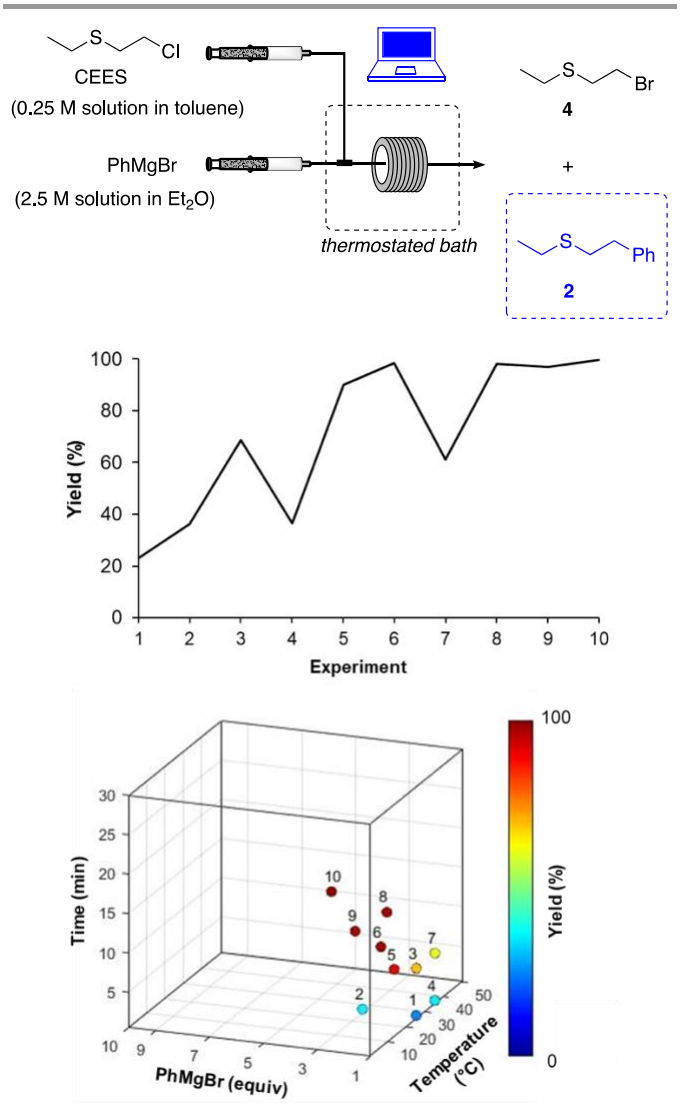

Figure 2. Schematic depiction of the flow system for the neutralization of CEES with PhMgBr (up), Maximization of the yield of 2 (middle), and representation of the three-dimensional experimental conditions of the optimization (down).

Since flow-through devices deliver a quantity of products proportional to their operating time, with obvious benefits on the scale-up of a reaction with toxic CWA and potentially pyrophoric organometallics, the neutralization of CEES was scaled-up on 2 g under the optimized conditions (t^R = 13.7 min, T = 33 °C, n_{equiv}(PhMgBr) = 4.7). Thus, with a continuous running time of ca. 26 h yperite simulant was fully converted into target product **2** without adjustment of the reaction conditions.

On a safety aspect, it has to be noticed that the reaction quench releases 3.7 equivalents of benzene/mol of CEES neutralized. If benzene is known to as a carcinogenic compound, it is however ca. 10 times less toxic than CEES and ca. 1000 times less toxic than yperite.[58] However, the toxicity of the effluent could be mitigated by including an additional downstream process, directly injecting CO_2 gas to form the innocuous benzoic acid.[24,30,33] Attention shall also be paid to the accumulation of flammable volatiles at the reactor outlet.

Conclusions

This work shows that the neutralisation of the mustard simulant CEES with PhLi and PhMgBr is effective in a flow system and faster than in a classical batch reactor. By using a black-box optimization algorithm, optimal settings to convert CEES into an innocuous substitution product were identified at a minimal experimental cost. The robustness of the flow process as demonstrated on a multi-gram scale-up experiment. Such an approach represents a much safer alternative to current batch processes and studies to propose an all-in-one flow device for on-site neutralisation are currently underway. Our future efforts will focus on the downstream part of the process to deliver a fully safe system.

Experimental section

General information

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents were used as supplied. The solvents were dried before use. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker Advance III 300 at 300 MHz and 76 MHz, respectively. Residual solvent peaks were used as the reference. Data for are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sex = sextet, sept = septet, m = multiplet), coupling constant (Hz) and integration). Chemical shifts are reported in ppm relative to the signals corresponding to residual non-deuterated solvent ($CDCl_3$: δ = 7.26 ppm for ^{1}H NMR and δ = 77.16 for ^{13}C NMR). Analyses were performed on GC-FID thermoscientific trace 1310 equipped with Durabond DB-5MS (30 m, 0.250 mm Ø narrowbore, 0.25 µm film), the He vector gas flow rate of 1 ml.min^{-1} in split mode (50 mL.min^{-1}) and the inlet injector temperature of 250 °C. As FID detector, the air flow rate is at 350 mL.min^{-1} with vector gas at 35 mL.min^{-1}. The temperature program was as follows, 5 minutes at 40 °C, then a temperature rate of 15 °C.min^{-1} until reach 150 °C. Then, it stays at 150 °C for 1 minute and at a temperature rate of 25 °C/min until reach 300 °C and holds at 300 °C for 5 minutes. The GC-MS analysis was performed by low resolution GC-MS (Thermo scientific, TRACE 1310 gas chromatography and ISQ 7000 single Quadrupole Mass spectrometer) (HP5- MS stationary phase, l = 30 cm, d = 0.25 mm, film thickness = 0.25 µm). The temperature program was as follows, 5 minutes at 40 °C, then a temperature rate of 15 °C.min^{-1} until reach 150 °C holds at 150 °C for 2 minutes. All GC-sample were prepared using grade HPLC solvents from Fischer. All fluidic tubing, connections, adapters were manufactured by IDEX Health and Science. Syringe pumps were manufactured by Harvard apparatus (Pump 11) with Air Tite plastic syringe. All details regarding the modified Nelder-Mead method used in this study can be found in reference [47].

Procedure for the flow neutralisation of CEES with PhMgBr to afford 1-ethylthio-2-phenylethane (2)

The flow system is composed of two 5 mL Air Tite plastic syringes, charged on two syringe pumps (Pump 11 Elite) and connected to a PEEK T-shaped mixer (90°) and a 0.79 mL PFA tubular microreactor (L = 100 cm, ID = 1 mm, OD = 1.59 mm) immersed in a bath thermostated at 33 °C. A solution of PhMgBr (2.5 M in diethyl ether) was injected in the first inlet (flow rate Q_1 = 19.2 µL.min^{-1}) and a solution of CEES (0.25 M) and decane as internal standard (0.125 M) in toluene in the second inlet (flow rate Q_2 = 38.1 µL.min^{-1}). The outlet of the reactor was collected in flask filled with ethanol. The reaction was monitored by GC-FID and confirmed by NMR analyses.

GC-FID (t_R = 14.84 min), GC-MS (t_R = 14.36 min).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16-7.35 (m, 5H), 2.84-2.93 (m, 2H), 2.73-2.83 (m, 2), 2.57 (q, *J* = 7.4, 2H), 1.27 (t, *J* = 7.4, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.7, 128.5, 126.3, 36.3, 33.2, 26.1, 14.8.

Author Contributions

The work was conceived by J.L.; conducted by V.B.S., S.M. and A.D. and supervised by J.L. F.X.F. initialized and supervised the algorithm. The manuscript was drafted and edited by J.L. and F.X.F and reviewed by J.L., F.X.F., V.B.S. and S.M. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Marine Soubiale is thanked for her kind help. This work has been partially supported by Université Rouen Normandie, INSA Rouen Normandie, Centre National de la Recherche Scientifique (CNRS), European Regional Development Fund (ERDF), Labex SynOrg (ANR-11-LABX-0029), Carnot Institute I2C, the graduate school for research XL-Chem (ANR-18-EUR-0020 XL CHEM) and by Région Normandie.

Notes and references

‡ The common acronym HD comes from World War I and standing for *Hunstuff Distilled* is still in use in scientific reports.

1 E. Oheix, E. Gravel and E. Doris, *Chemistry – A European Journal*, 2021, **27**, 54–68.
2 S. Y. Bae and M. D. Winemiller, *J. Org. Chem.*, 2013, **78**, 6457–6470.
3 C. A. S. Brevett, K. B. Sumpter and R. G. Nickol, *Journal of Hazardous Materials*, 2009, **162**, 281–291.
4 Y. J. Jang, K. Kim, O. G. Tsay, D. A. Atwood and D. G. Churchill, *Chem. Rev.*, 2015, **115**, PR1–PR76.
5 B. Picard, I. Chataigner, J. Maddaluno and J. Legros, *Org. Biomol. Chem.*, 2019, **17**, 6528–6537.
6 K. Vellingiri, L. Philip and K.-H. Kim, *Coordination Chemistry Reviews*, 2017, **353**, 159–179.
7 S. S. Mondal and H.-J. Holdt, *Angew. Chem. Int. Ed.*, 2016, **55**, 42–44.
8 S. Mansour, V. B. Silva, E. S. Orth and J. Legros, *Org. Biomol. Chem.*, 2022, **20**, 7604–7608.
9 T. H. Mahato, G. K. Prasad, B. Singh, K. Batra and K. Ganesan, *Microporous and Mesoporous Materials*, 2010, **132**, 15–21.

10 F. Carniato, C. Bisio, R. Psaro, L. Marchese and M. Guidotti, *Angew. Chem. Int. Ed.*, 2014, **53**, 10095–10098.
11 J. Dong, J. Hu, Y. Chi, Z. Lin, B. Zou, S. Yang, C. L. Hill and C. Hu, *Angew. Chem. Int. Ed.*, 2017, **56**, 4473–4477.
12 J. R. Hiscock, G. P. Bustone and E. R. Clark, *ChemistryOpen*, 2017, **6**, 497–500.
13 A. Converso, P.-L. Saaidi, K. B. Sharpless and M. G. Finn, *J. Org. Chem.*, 2004, **69**, 7336–7339.
14 F. M. Akwi and P. Watts, *Chem. Commun.*, 2018, **54**, 13894–13928.
15 M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chemical Reviews*, 2017, **117**, 11796–11893.
16 R. Gérardy, N. Emmanuel, T. Toupy, V.-E. Kassin, N. N. Tshibalonza, M. Schmitz and J.-C. M. Monbaliu, *European Journal of Organic Chemistry*, 2018, **2018**, 2301–2351.
17 J.-C. M. Monbaliu and J. Legros, *Lab Chip*, 2023, **23**, 1349–1357.
18 M. Guidi, P. H. Seeberger and K. Gilmore, *Chemical Society Reviews*, 2020, **49**, 8910–8932.
19 M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley and C. V. Stevens, *Chem. Soc. Rev.*, 2016, **45**, 4892–4928.
20 H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami and J. Yoshida, *J. Am. Chem. Soc.*, 2007, **129**, 3046–3047.
21 H. Kim, A. Nagaki and J. Yoshida, *Nature Communications*, 2011, **2**, 264.
22 H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim and J. Yoshida, *Science*, 2016, **352**, 691–694.
23 A. Nagaki, D. Ichinari and J. Yoshida, *J. Am. Chem. Soc.*, 2014, **136**, 12245–12248.
24 A. Nagaki, Y. Takahashi and J. Yoshida, *Chem. Eur. J.*, 2014, **20**, 7931–7934.
25 G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, T. Langer, L. Degennaro, V. Pace and R. Luisi, *J. Am. Chem. Soc.*, 2017, **139**, 13648–13651.
26 P. Musci, M. Colella, A. Sivo, G. Romanazzi, R. Luisi and L. Degennaro, *Org. Lett.*, 2020, **22**, 3623–3627.
27 M. Colella, A. Tota, Y. Takahashi, R. Higuma, S. Ishikawa, L. Degennaro, R. Luisi and A. Nagaki, *Angewandte Chemie International Edition*, 2020, **59**, 10924–10928.
28 A. Hafner, V. Mancino, M. Meisenbach, B. Schenkel and J. Sedelmeier, *Org. Lett.*, 2017, **19**, 786–789.
29 A. Hafner, P. Filipponi, L. Piccioni, M. Meisenbach, B. Schenkel, F. Venturoni and J. Sedelmeier, *Org. Process Res. Dev.*, 2016, **20**, 1833–1837.
30 K. Pérez, S. Leveneur, F. Burel, J. Legros and D. Vuluga, *React. Chem. Eng.*, 2023, **8**, 432–441.
31 T. P. Petersen, M. R. Becker and P. Knochel, *Angew. Chem. Int. Ed.*, 2014, **53**, 7933–7937.
32 M. A. Ganiek, M. R. Becker, M. Ketels and P. Knochel, *Org. Lett.*, 2016, **18**, 828–831.
33 J. Wu, X. Yang, Z. He, X. Mao, T. A. Hatton and T. F. Jamison, *Angew. Chem. Int. Ed.*, 2014, **53**, 8416–8420.
34 M. Colella, A. Nagaki and R. Luisi, *Chemistry – A European Journal*, 2020, **26**, 19–32.
35 M. Power, E. Alcock and G. P. McGlacken, *Organic Process Research & Development*, 2020, **24**, 1814-1838.
36 A. Nagaki, *Tetrahedron Letters*, 2019, **60**, 150923.
37 B. Picard, B. Gouilleux, T. Lebleu, J. Maddaluno, I. Chataigner, M. Penhoat, F.-X. Felpin, P. Giraudeau and J. Legros, *Angew. Chem. Int. Ed.*, 2017, **56**, 7568–7572.
38 A. Delaune, S. Mansour, B. Picard, P. Carrasqueira, I. Chataigner, L. Jean, P.-Y. Renard, J.-C. M. Monbaliu and J. Legros, *Green Chem.*, 2021, **23**, 2925–2930.
39 N. Emmanuel, P. Bianchi, J. Legros and J.-C. M. Monbaliu, *Green Chem.*, 2020, **22**, 4105–4115.
40 V.-E. H. Kassin, D. V. Silva-Brenes, T. Bernard, J. Legros and J.-C. M. Monbaliu, *Green Chem.*, 2022, **24**, 3167–3179.
41 B. M. Sharma, S.-J. Yim, A. Nikam, G.-N. Ahn and D.-P. Kim, *React. Chem. Eng.*, 2021, **6**, 1454–1461.
42 G. Hamdoun, M. Sebban, E. Cossoul, A. Harrison-Marchand, J. Maddaluno and H. Oulyadi, *Chem. Commun.*, 2014, **50**, 4073–4075.
43 O. Tai, R. Hopson and P. G. Williard, *Org. Lett.*, 2017, **19**, 3966–3969.
44 G. Barozzino-Consiglio, G. Hamdoun, C. Fressigné, A. Harrison-Marchand, J. Maddaluno and H. Oulyadi, *Chemistry – A European Journal*, 2017, **23**, 12475–12479.
45 H. Oulyadi, *Synthesis*, 2018, **50**, 3603–3614.
46 T. Wirth, *Angew. Chem. Int. Ed.*, 2017, **56**, 682–684.
47 D. Cortés-Borda, K. V. Kutonova, C. Jamet, M. E. Trusova, F. Zammattio, C. Truchet, M. Rodriguez-Zubiri and F.-X. Felpin, *Org. Process Res. Dev.*, 2016, **20**, 1979–1987.
48 N. Vasudevan, E. Wimmer, E. Barré, D. Cortés-Borda, M. Rodriguez-Zubiri and F. Felpin, *Adv. Synth. Catal.*, 2021, **363**, 791–799.
49 J. P. McMullen, M. T. Stone, S. L. Buchwald and K. F. Jensen, *Angewandte Chemie International Edition*, 2010, **49**, 7076–7080.
50 O. J. Kershaw, A. D. Clayton, J. A. Manson, A. Barthelme, J. Pavey, P. Peach, J. Mustakis, R. M. Howard, T. W. Chamberlain, N. J. Warren and R. A. Bourne, *Chemical Engineering Journal*, 2023, **451**, 138443.
51 V. Sans, L. Porwol, V. Dragone and L. Cronin, *Chem. Sci.*, 2015, **6**, 1258–1264.
52 A. D. Clayton, L. A. Power, W. R. Reynolds, C. Ainsworth, D. R. J. Hose, M. F. Jones, T. W. Chamberlain, A. J. Blacker and R. A. Bourne, *J Flow Chem*, 2020, **10**, 199–206.
53 D. E. Fitzpatrick, C. Battilocchio and S. V. Ley, *Org. Process Res. Dev.*, 2016, **20**, 386–394.
54 H.-W. Hsieh, C. W. Coley, L. M. Baumgartner, K. F. Jensen and R. I. Robinson, *Org. Process Res. Dev.*, 2018, **22**, 542–550.
55 P. Mueller, A. Vriza, A. D. Clayton, O. S. May, N. Govan, S. Notman, S. V. Ley, T. W. Chamberlain and R. A. Bourne, *React. Chem. Eng.*, 2023, **8**, 538–542.
56 E. C. Aka, E. Wimmer, E. Barré, N. Vasudevan, D. Cortés-Borda, T. Ekou, L. Ekou, M. Rodriguez-Zubiri and F.-X. Felpin, *J. Org. Chem.*, 2019, **84**, 14101–14112.
57 D. Cortés-Borda, E. Wimmer, B. Gouilleux, E. Barré, N. Oger, L. Goulamaly, L. Peault, B. Charrier, C. Truchet, P. Giraudeau, M. Rodriguez-Zubiri, E. Le Grognec and F.-X. Felpin, *J. Org. Chem.*, 2018, **83**, 14286–14299.
58 LD_{50} (oral, rat) in mg/kg. Benzene: 2000 mg/kg; CEES: 252 mg/kg; Yperite: 2.4 mg/kg.