Published in final edited form as:

Org Process Res Dev. 2018 August 17; 22(8): 971–977. doi:10.1021/acs.oprd.8b00113.

Continuous Platform to Generate Nitroalkanes On-Demand (in situ) using Peracetic Acid-Mediated Oxidation in a PFA Pipes-in-Series Reactor

Sergey V. Tsukanov^{*,†,‡}, Martin D. Johnson[†], Scott A. May[†], Stanley P. Kolis[†], Matthew H. Yates[†], and Jeffrey N. Johnston^{*,‡}

[†]Small Molecule Design and Development, Eli Lilly and Company, Indianapolis, Indiana 46285, United States

[‡]Department of Chemistry and Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, Tennessee 37235, United States

Abstract

The synthetic utility of the aza-Henry reaction can be diminished on scale by potential hazards associated with the use of peracid to prepare nitroalkane substrates, and the nitroalkanes themselves. In response, a continuous and scalable chemistry platform to prepare aliphatic nitroalkanes on-demand is reported, using the oxidation of oximes with peracetic acid and direct reaction of the nitroalkane intermediate in an aza-Henry reaction. A uniquely designed pipes-in-series plug flow tube reactor addresses a range of process challenges including stability and safe handling of peroxides and nitroalkanes. The subsequent continuous extraction generates a solution of purified nitroalkane which can be directly used in the following enantioselective aza-Henry chemistry to furnish valuable chiral diamine precursors in high selectivity, thus, completely avoiding isolation of potentially unsafe low molecular weight nitroalkane intermediate. A continuous campaign (16 h) established that these conditions were effective in processing 100 g of the oxime and furnishing 1.4 L of nitroalkane solution.

TOC graphic

*Corresponding author tsukanov_sergey_vladimirovich@lilly.com, jeffrey.n.johnston@vanderbilt.edu.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.

Experimental procedures for oxime, nitroalkane synthesis and aza-Henry reaction, NMR spectra of key compounds, continuous equipment, set up and procedure, microcalorimetry and ARC data for 1-(*tert*-butyl)-4-(nitromethyl)benzene.

Notes

The authors declare no competing financial interest.

Keywords

nitroalkane; peroxide; pipes-in-series reactor; sustainable or green chemistry; continuous processing; flow chemistry

INTRODUCTION

Aliphatic nitroalkanes are highly useful synthetic intermediates which can be utilized in a variety of organic transformations and serve as valuable precursors to chiral amines¹. Amines², diamines³, α -amino acids⁴, α -amino phosphonates⁵ derived from a nitro group are also key intermediates in therapeutic development.⁶ Despite their established utility, nitroalkanes remain generally underutilized in industrial settings due to the safety risks associated with nitro group. There are several research examples which address the issue of nitro functional group in chemical transformations by application of flow chemistry.⁷ Flow technologies offer a safer and improved alternative to batch reactions by reducing quantities of nitroalkanes in the reactor where it may be under forcing conditions. Additional advantages of a continuous format include improved heat transfer and temperature control for exothermic transformations, and minimization of solvent, resulting in an overall greener, cost effective, and often more reliable process.⁸ While numerous publications have detailed the use of nitroalkanes in flow reactors, very little attention has been paid to the safety risks associated with batch handling, storing and processing large volumes of low molecular weight nitroalkane when it is used as a starting material, intermediate, or product. For example, there are potential risks associated with the use of large feeding and collecting vessels at kilogram-scale. When applied to a potentially hazardous nitroalkane, their concentration and isolation steps become no less important than the safety of the chemical reaction itself, even at relatively small scale. Approaches that minimize nitroalkane quantities through a continuous recycle have been published,⁹ however no examples exist that detail the synthesis and immediate reaction of nitroalkanes. A general safety assessment and the development of an innovative strategy to provide comprehensive solutions to these challenges are therefore highly valuable. This report describes the development of a flexible platform for the safe and reliable preparation, purification and downstream transformation of nitroalkane intermediates. The nature of the process provides on-demand nitroalkane access without isolation by a safe and straightforward continuous format, one that can be further grown in scale.

We recently reported a scale-up procedure to conduct an enantioselective aza-Henry reaction using semi-continuous conditions,¹⁰ an investigation that required large quantities of aliphatic nitroalkanes. A literature search of nitroalkane preparations led to the conclusion that efficient and high yielding methods to generate nitroalkanes on large-scale are rather limited.¹¹ The most commonly utilized method is a direct substitution of the corresponding alkyl halide with sodium nitrite as a nucleophile.¹² This mild procedure uses a simple and convenient nitrite source and inexpensive halides has certain advantages for small-scale preparations. However, due to the ambident nature of nitrite it results in larger quantities of the corresponding nitrite *O*-alkylation product during scale up, requiring tedious chromatographic purifications.¹³ Most recently developed alternatives, while being valuable

additions, remain impractical from safety and economical standpoints (Scheme 1).^{14,15} Despite the fact that scaling large amounts of MCPBA was not a suitable strategy, the general approach of oxime oxidation was attractive due to its simplicity and cost efficiency.¹⁰ Oximes are readily available starting materials which can be prepared in one step using hydroxylamine and a wide variety of aldehydes. Further investigation of oxime oxidations using peroxide reagents has shown that it is a well-known transformation with multiple literature precedents.¹⁶ Among alternative oxidants considered, a solution of peracetic acid offers the benefits of low molecular weight, low cost, and ease of removal from the product stream (base wash), in addition to a favorable safety profile among peracids.¹⁷ After careful analysis we came to a conclusion that reaction using peracetic acid solution could serve as the most practical option for the scale up and further development.

RESULTS AND DISCUSSION

We initiated our study with a detailed look at the oxidant for the process. Peracetic acid is a commercially available and relatively inexpensive peracid. However, a solution of this reagent represents an equilibrium mixture of peroxy acid, hydrogen peroxide, water and acetic acid. Furthermore, the peracid is relatively unstable and degrades at room temperature (*via* reversible reaction to hydrogen peroxide and acetic acid) with a rate of ~1–2% over 24 hours.¹⁸ The recommended storing condition for peracetic acid is at 2–8 °C, significantly reducing the degradation pathway (to ~0.3% a day) but not eliminating it. Finally, peracetic acid is a highly reactive and hazardous material with a variety of risks related to its usage (HMIS: Health: 3, Flammability: 2, Reactivity: 4). The safety and stability of this reagent not only creates additional challenges for storing and handling but also affects the quality and reliability of the oxidation process. To avoid these problems we envisioned an *in situ* continuous generation of peracetic acid.

The most common way to generate this reagent is reaction of acetic acid and hydrogen peroxide under acid catalysis.¹⁷ These conditions also require distillation of the product in order to reach the desired concentration. An alternative and simpler protocol *via* ion-exchange resin (Amberlite IR-120) catalyzed process was also reported in literature.¹⁹ Using 10–20% mass of the resin at 50 °C we could generate 15 mass % solution in a 3 hour period with a maximum concentration of 16.5 mass % (~60–63% yield) reached after 24 hours. With these encouraging results we pursued this transformation under continuous conditions in a packed bed reactor. A 20" (508 mm) tall PFA (perfluoroalkoxy copolymer resin) tube-in-tube reactor with 15" (381 mm) heated zone was packed with ~18 g of the resin, and using 1 mL/min flow rates (~6 minute residence time) in 2 h we were able reach a steady state and produce peracetic acid solution with 16.5 mass % concentration. The packed bed reactor was used intermittently over a 5 month period of time with overall run time over 80 h consistently generating peracetic acid with maximal equilibrium concentration and without any sign of activity deterioration or decline in activity.

With this reliable source of peracid reagent, a preliminary evaluation of the oxime oxidation reaction was made using a traditional approach in batch. The corresponding oxime (20.0 mmol scale) was dissolved in acetic acid, heated to 90 °C, and then treated with peracetic acid in dropwise fashion (over 20–30 minutes). Not unexpectedly, the reaction was

dependent on the electronic nature of the substrate. Reactions of aromatic substrates with electron donating groups (Table 1, entries 9–12) proceeded in a rapid fashion and the temperature of the reaction strongly depended on the rate of the peroxide addition. Furthermore, due to the exothermic nature of the process, proper temperature control was identified as a potential challenge for scale-up. For aromatic oximes with electron withdrawing substituents (Table 1, entries 2–5), the kinetics of the reaction were slower, and conditions with two additional equivalents of peracetic acid were therefore utilized. A wide variety of nitroalkanes with both electron rich and electron deficient phenyl rings was successfully prepared. Aliphatic (Table 1, entries 6–8) and secondary nitroalkanes (Table 1, entries 15–16) could be generated in reasonable yields. The oxidation of ketoximes is notable, as these are known to be recalcitrant substrates. Further optimization of the reaction conditions for each substrate could be beneficial to achieve optimal yield, especially with volatile low molecular weight nitroalkanes. In situ generated peracetic acid showed results similar to the commercial peracetic acid.²⁰ Since the commercial oxidant is more concentrated the reaction resulted in higher yields for electron poor substrates, but in contrast, more diluted acid generated by ion exchange catalysis provided better outcomes with electron rich substrates.

In order to understand the potential thermal risks presented by the oxidation of oximes to nitroalkanes in a batch reactor, calorimetry studies were executed to (a) assess the thermal stability of the reactants (oxime and peracetic acid) and product (nitroalkane) as well as (b) to assess the energy liberated during the oxidation reaction (See SI for the detailed results). Peracetic acid decomposition has also been studied in detail by Wang²¹. Differential Scanning Calorimetry (DSC) for peracetic acid solutions shows two low onset exotherms (38–41 °C and 83–102 °C) and enthalpy of decomposition in a wide range from 556–1503 J/g. This data clearly demonstrates the energetic nature of this material. Both oxime and nitroalkane also have low onsets (223 and 142 °C correspondingly) and high decomposition energetics (> 300 J/g) which prompts further studies to determine explosive behavior.

The energetics of the semi-batch oxidation reaction was studied using a Thermal Hazard Technology power compensation microcalorimeter, and the reaction safety was evaluated using the method of Stoessel²² for reaction criticality class determination (Figure 1). The heat of the reaction was determined to be –112.8 J/g for the reaction mass and adiabatic temperature rise was calculated at +99°C. On its own this would be enough to classify this reaction as “medium risk” from the Stoessel criticality perspective. The calculated maximum temperature of the synthesis reaction (MTSR, 189 °C), would likely not be reached, as the boiling point of the acetic acid solvent (118–119 °C) would prevent the reaction from reaching this temperature. However, two exothermic onsets for peracetic acid that occur below the process temperature, and one that occurs just above the MTT (maximum temperature for technical reasons) cause this reaction to be dangerous in the batch or semi-batch mode of operation. From the perspective of batch chemistry on scale, this oxidation clearly represents a high risk. Therefore, development of an alternative continuous synthetic procedure that incorporates engineering controls was pursued.

After evaluating substrates we turned our attention to development of a continuous oxidation. We started the process utilizing two separate feeds: 2.2 M solution of peracetic

acid and 1.35 M solution of 4-*tert*-butylbenzaldehyde oxime in acetic acid. Solutions were mixed together and pumped through 2.5 mL stainless steel plug flow reactor (PFR) at 90–95 °C (heated in a GC oven). The pressure control was achieved by a standard membrane back-pressure regulator. However, despite multiple attempts with a residence time varied from 3 to 30 min, very little nitroalkane was formed under these conditions (Table 2).

The major products isolated from the reaction were the corresponding benzoic acid) and aldehyde with varying amounts of starting material oxime and nitrile. Gas pockets were observed at the outlet of the reactor highlighting incompatibility of the peroxide reagent with the metal surface of the reactor. Substituting the metal PFR with a PFA PFR resulted in a slightly improved result, with nitroalkane and benzoic acid representing the major products of the process. A second difference between a PFR and an open flask reaction is the overhead space. It was noted that in the PFA reactor fitted with a back pressure regulator large amounts of gas generated in a process would be trapped inside the reaction mixture, but could otherwise easily escape in a batch scenario with headspace. The literature also confirmed that peracetic acid can spontaneously decompose, generating oxygen²³ that might over-oxidize the reaction intermediates leading to increased amounts of benzoic acid. A test reaction conducted in a closed vessel (port connector)²⁴ with a limited amount of the overhead space supported this hypothesis as evidenced by an improved nitroalkane yield relative to the regular metal PFR.

To address these issues of material incompatibility and generation of gaseous products, we designed a novel PFA pipes-in-series reactor. The principal idea of a pipes-in-series reactor constructed from the metal was described previously and successfully applied for the chemical processes where gas transport is a critical factor²⁵, and where the reaction requires gas-liquid contact and long reaction times.²⁶ In the same manner the PFA version consists of pipes ($d = 0.8$ cm, $V = 3.2$ – 3.3 mL per pipe) and PFA jumper tubes connecting the pipes ($d = 1.6$ mm, $V = 0.05$ to 0.5 mL per connecting tube). The reaction mixture spends the majority of its residence time inside the pipes (~85% liquid filled) while a neutral gas carrier (nitrogen) enables mixing inside the pipes and carries small liquid slugs through jumpers into the next pipe while providing effective gas/liquid mixing. The major role of the carrier gas in this application is to remove oxygen and other gaseous products from the reaction mixture. Alternative solutions to entrapment of the gases in reaction by switching to continuous stirred tank reactor or using unique annular flow regime in PFR have been successfully utilized.²⁷

We tested a 4-pipes reactor (12 mL) at 95 °C with a 30 minute (mean) residence time. Immediate improvement was noted with ~69% of nitroalkane as a major product, coinciding with a reduced quantity of benzoic acid (~28%). Taking into account the instability of the starting material, the peracetic acid feed was initially divided into two equal streams, and then into four equal streams introduced between the pipes. The ratio of nitroalkane was improved to 80%, and only 10–12% of benzoic acid was registered. The larger reactor (42 mL, 16 pipes) was next designed, and in this reactor the jumpers containing addition T's were removed from the heating bath to ensure minimal heat exposure and decomposition of the unstable oxidant prior to entering the pipes. Kinetic studies were also performed in order to determine the best splitting of the peracetic acid feed. The 60% upfront and 13.3% after

4th, 8th and 12th pipes was the most successful distribution of the reagent giving maximum product (82–85%) and minimal amounts of starting material (3–5%) and benzoic acid (12–13%).

The resulting nitroalkane mixture was subjected to a continuous extraction with toluene as an organic phase which included three mixer-settler stages. The second stage (vessel II) in the mixer-settler process was a water wash to remove acetic acid, and the third stage (vessel III) was a sodium hydroxide wash to remove the rest of acetic acid and also benzoic acid by-product. The first stage (vessel I) was back extraction of the water layer with fresh toluene in order to prevent loss of the material to the water waste. The first and second stages operated in counter-current fashion to minimize waste loss to the aqueous phase. The toluene played a dual role in the high-yield nitroalkane recovery. In this solvent, deprotonation of nitroalkane by the base was relatively slow, leading to selective carboxylic acid extraction. Use of heptane instead gives complete loss of nitroalkane to the base layer.

Furthermore the toluene solution of nitroalkane could be directly used in the following aza-Henry chemistry²⁸ without further manipulation or addition of an isolation procedure, thereby producing the desired product in 89–91% ee after 3 hours. The crude solution reactivity under MAM (Mono- AMidine) catalysis when compared to the purified material was indistinguishable.

Several major challenges were considered while developing an oxime oxidation process (Figure 2). The exothermic reaction at elevated temperatures (90–100 °C) proceeds with a significant heat release and requires several equivalents of peroxide as a reagent while producing nitroalkane product. The newly developed continuous platform not only delivered appropriate solutions to all these questions (Figure 2) but also provided extensive opportunities related to application of the flow chemistry with labile and unstable reagents and chemistry of peroxides and nitroalkanes.

CONCLUSIONS

In summary we have a new platform to prepare a major class of nitroalkanes that offers an effective and general strategy for the safe and controlled preparation/utilization of nitroalkane compounds on an industrially-relevant scale. This approach benefits from a synthesis of nitroalkanes from simple and inexpensive starting materials and an option to *in situ* utilize them without isolation or additional purification of potentially hazardous intermediates. A simple PFA packed bed and PFA pipes-in-series reactors provide distinctive qualities to the system enabling the use of labile reagents at high temperatures. An opportunity to combine this platform with flow aza-Henry chemistry gives a direct alternative for the short enantioselective synthesis of widespread and impactful chiral diamines and their valued derivatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We gratefully acknowledge support from the Lilly Innovation Fellowship Award (LIFA) for SVT. The authors also thank Richard Miller for his extensive help with the continuous campaigns. Catalyst development was supported by funding from the National Institutes of Health (GM 084333).

REFERENCES

1. (a) Ono N in *The Nitro Group in Organic Synthesis* John Wiley & Sons, Inc., New York, USA, 2001.(b) Feuer H, Nielsen H, A. T. Eds. *Nitro Compounds: Recent Advances in Synthesis and Chemistry*; VCH Publishers: New York, 1990.
2. (a) Rezazadeh S; Devannah V; Watson DA Nickel-Catalyzed C-Alkylation of Nitroalkanes with Unactivated Alkyl Iodides, *J. Am. Chem. Soc* 2017, 139, 8110. [PubMed: 28594543] (b) Hughes DL Patent Review of Manufacturing Routes to Recently Approved PARP Inhibitors: Olaparib, Rucaparib, and Niraparib, *Org. Proc. Res. Dev* 2017, 21, 1227.
3. Noble A; Anderson JC Nitro-Mannich Reaction, *Chem. Rev* 2013, 113, 2887. [PubMed: 23461586]
4. (a) Moreau B; Charette AB Expedient Synthesis of Cyclopropane α -Amino Acids by the Catalytic Asymmetric Cyclopropanation of Alkenes Using Iodonium Ylides Derived from Methyl Nitroacetate, *J. Am. Chem. Soc* 2005, 127, 18014. [PubMed: 16366547] (b) Li H; Wang Y; Tang L; Wu FH; Liu XF; Guo CY; Foxman BM; Deng L Stereocontrolled Creation of Adjacent Quaternary and Tertiary Stereocenters by a Catalytic Conjugate Addition, *Angew. Chem., Int. Ed.* 2004, 44, 105. [PubMed: 15565669] (c) Knudsen KR; Jorgensen KA A chiral molecular recognition approach to the formation of optically active quaternary centres in aza-Henry reactions, *Org. Biomol. Chem* 2005, 3, 1362. [PubMed: 15827627] (d) Shen B; Johnston JN A Formal Enantioselective Acetate Mannich Reaction: The Nitro Functional Group as a Traceless Agent for Activation and Enantiocontrol in the Synthesis of β -Amino Acids, *Org. Lett* 2008, 10, 4397. [PubMed: 18798639]
5. (a) Wilt JC; Pink M; Johnston JN A diastereo- and enantioselective synthesis of α -substituted anti- α,β -diaminophosphonic acid derivatives, *Chem. Commun* 2008, 35, 4177.(b) Blaszczyk R; Gajda A; Zawadzki S; Czubacka E; Gajda T *N*-Carbamate α -aminoalkyl-p-tolylsulfones—convenient substrates in the nitro-Mannich synthesis of secondary *N*-carbamate protected syn-2-amino-1-nitroalkanephosphonates, *Tetrahedron* 2010, 66, 9840.
6. (a) Davis T; Vilgelm AE; Richmond A; Johnston JN Preparation of (–)-Nutlin-3 Using Enantioselective Organocatalysis at Decagram Scale, *J. Org. Chem* 2013, 78, 10605. [PubMed: 24127627] (b) Dobish MC; Villalta F; Waterman MR; Lepesheva GI; Johnston JN Organocatalytic, Enantioselective Synthesis of VNI: A Robust Therapeutic Development Platform for Chagas, a Neglected Tropical Disease, *Org. Lett* 2012, 14, 6322. [PubMed: 23214987] (c) Davis T; Danneman M; Johnston JN Chiral proton catalysis of secondary nitroalkane additions to azomethine: synthesis of a potent GlyT1 inhibitor, *Chem. Commun* 2012, 48, 5578.(d) Hynes PS; Stupp PA; Dixon DJ Organocatalytic Asymmetric Total Synthesis of (R)-Rolipram and Formal Synthesis of (3S,4R)-Paroxetine, *Org. Lett* 2008, 10, 1389. [PubMed: 18324820] (e) Weng J; Li Y-B; Wang R-B; Li F-Q; Liu C; Chan ASC; Lu GL A Practical and Azide-Free Synthetic Approach to Oseltamivir from Diethyl *d*-Tartrate, *J. Org. Chem* 2010, 75, 3125. [PubMed: 20394411] (f) Xie H; Zhang Y; Zhang S; Chen X; Wang W Bifunctional Cinchona Alkaloid Thiourea Catalyzed Highly Efficient, Enantioselective Aza-Henry Reaction of Cyclic Trifluoromethyl Ketimines: Synthesis of Anti-HIV Drug DPC 083, *Angew. Chem., Int. Ed.* 2011, 50, 11773. [PubMed: 21989976] (g) Handa S; Gnanadesikan V; Matsunga S; Shibasaki MJ Heterobimetallic Transition Metal/Rare Earth Metal Bifunctional Catalysis: A Cu/Sm/Schiff Base Complex for Syn-Selective Catalytic Asymmetric Nitro-Mannich Reaction, *J. Am. Chem. Soc* 2010, 132, 4925. [PubMed: 20218689]
7. (a) Tsubogo T; Oyamada H; Kobayashi S Multistep continuous-flow synthesis of (R)- and (S)-rolipram using heterogeneous catalysts, *Nature*, 2015, 520, 329. [PubMed: 25877201] (b) Ghislieri, D.; Gilmore, K.; Seeberger, P. H. Chemical Assembly Systems: Layered Control for Divergent, Continuous, Multistep Syntheses of Active Pharmaceutical Ingredients, *Angew. Chem., Int. Ed.* 2015, 54, 678. [PubMed: 25414136] (c) Rossi S; Benaglia M; Puglisi A; De Filippo CC; Maggini M Continuous-Flow Stereoselective Synthesis in Microreactors: Nucleophilic Additions to Nitrostyrenes Organocatalyzed by a Chiral Bifunctional Catalyst, *J. Flow Chem* 2015, 5, 17.(d) Braune S; Pöchlauer P; Reintjens R; Steinhof S; Winter M; Lobet O; Guidat R; Woehl P;

- Guermeur C Selective nitration in a microreactor for pharmaceutical production under cGMP conditions, *Chim. Oggi-Chem Today*, 2009, 27, 26.(e) Knapkiewicz P; Skowerski K; Jaskolska DE; Barbasiewicz M; Olszewski TK Nitration Under Continuous Flow Conditions: Convenient Synthesis of 2-Isopropoxy-5-nitrobenzaldehyde, an Important Building Block in the Preparation of Nitro-Substituted Hoveyda–Grubbs Metathesis Catalyst, *Org. Proc. Res. Dev* 2012, 16, 1430.(f) Cantillo D; Damm M; Dallinger D; Bauser M; Berger M; Kappe CO Sequential Nitration/Hydrogenation Protocol for the Synthesis of Triaminophloroglucinol: Safe Generation and Use of an Explosive Intermediate under Continuous-Flow Conditions, *Org. Proc. Res. Dev* 2014, 18, 1360.
8. For reviews see: Malet-Sanz L; Susanne F Continuous Flow Synthesis. A Pharma Perspective, *J. Med. Chem* 2012, 55, 4062. [PubMed: 22283413] Hartman RL; McMullen JP; Jensen KF Deciding Whether To Go with the Flow: Evaluating the Merits of Flow Reactors for Synthesis, *Angew. Chem., Int. Ed.* 2012, 51, 7502. Tsubogo T; Ishiwata T; Kobayashi S Asymmetric Carbon–Carbon Bond Formation under Continuous-Flow Conditions with Chiral Heterogeneous Catalysts, *Angew. Chem, Int. Ed.* 2013, 52, 6590. [PubMed: 23720303] Mak XY; Laurino P; Seeberger PH Asymmetric reactions in continuous flow, *Beilstein J. Org. Chem* 2009, 5, 19. [PubMed: 19478913] Wegner J; Ceylan S; Kirschning A Flow Chemistry – A Key Enabling Technology for (Multistep) Organic Synthesis, *Adv. Synth. Cat* 2012, 354, 17. Mason BP; Price KE; Steinbacher JL; Bogdan AR; McQuade DT Greener Approaches to Organic Synthesis Using Microreactor Technology, *Chem. Rev* 2007, 107, 2300. [PubMed: 17373852] Ley SV On Being Green: Can Flow Chemistry Help? *The Chem. Record* 2012, 12, 378. [PubMed: 22711555] Gutmann B; Cantillo D; Kappe CO Continuous-Flow Technology—A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients, *Angew. Chem, Int. Ed.* 2015, 54, 6688. [PubMed: 25989203]
9. (a) Robergel DM; Noti C; Irle E; Eyholzer M; Rittiner B; Penn G; Sedelmeier G; Schenkel B Control of Hazardous Processes in Flow: Synthesis of 2-Nitroethanol, *J. Flow Chem* 2014, 4, 26.(b) Chentsova A; Ushakov DB; Seeberger PH; Gilmore K Synthesis of α -Nitro Carbonyls via Nitrations in Flow, *J. Org. Chem* 2016, 81, 9415. [PubMed: 27598836]
10. Tsukanov SV; Johnson MD; May SA; Rosemeyer M; Watkins MA; Kolis SP; Yates MH; Johnston JN Development of an Intermittent-Flow Enantioselective Aza-Henry Reaction Using an Arylnitromethane and Homogeneous Brønsted Acid–Base Catalyst with Recycle, *Org. Process Res. Dev* 2016, 20, 215. [PubMed: 27065720]
11. (a) Feuer H; Lawrence JP Alkyl nitrate nitration of active methylene compounds. IX. Nitration of alkyl substituted heterocyclic compounds, *J. Org. Chem* 1972, 37, 3662.(b) Feuer H; Friedman H Alkyl nitrate nitration of active methylene compounds. XI. Nitration of toluenes. Facile preparation of stilbenes, *J. Org. Chem* 1975, 40, 187.(c) Black AP; Babers FH Phenylnitromethane, *Org. Synth* 1939, 19, 73.(d) Hauser FH; Baghdanov VM Convenient preparation of ring-methoxylated phenylnitromethanes, *J. Org. Chem* 1988, 53, 2872.(e) Kurz ME; Ngoviwatchai P; Tantrarat T Nitroalkylation of aromatic hydrocarbons promoted by manganese(III) acetate, *J. Org. Chem* 1981, 46, 4668.(f) Vogl EM; Buchwald SL Palladium-Catalyzed Monoarylation of Nitroalkanes, *J. Org. Chem* 2002, 67, 106. [PubMed: 11777446]
12. Kornblum N; Larson HO; Blackwood RK; Mooberry DD; Oliveto EP; Graham GE A New Method for the Synthesis of Aliphatic Nitro Compounds, *J. Am. Chem. Soc* 1956, 78, 1497.
13. Davis T; Vilgelm AE; Richmond A; Johnston JN Preparation of (–)-Nutlin-3 Using Enantioselective Organocatalysis at Decagram Scale, *J. Org. Chem* 2013, 78, 10605. [PubMed: 24127627]
14. Walvoord RR; Berritt S; Kozlowski MC Palladium-Catalyzed Nitromethylation of Aryl Halides: An Orthogonal Formylation Equivalent, *Org. Lett* 2012, 14, 4086. [PubMed: 22839593]
15. Vara B; Mayasundari A; Tellis J; Danneman M; Arredondo V; Davis T; Min J; Finch K; Guy RK; Johnston JN Organocatalytic, Diastereo- and Enantioselective Synthesis of Nonsymmetric *cis*-Stilbene Diamines: A Platform for the Preparation of Single-Enantiomer *cis*-Imidazolines for Protein–Protein Inhibition, *J. Org. Chem* 2014, 79, 6913. [PubMed: 25017623]
16. Emmons WD; Pagano AS Peroxytrifluoroacetic Acid. VI. The Oxidation of Oximes to Nitroparaffins, *J. Am. Chem. Soc* 1957, 77, 4557.
17. Oxime oxidation has been evaluated using a broad range of oxidants, often at elevated temperature including peracids: (a) [16]. Stiefel J Synthesis of 2-phenyl-1,3-propanediol. U.S. Patent 5,056,072 Dec. 10, 1991. Bose DS; Vanajatha G A Versatile Method for the Conversion of Oximes to Nitroalkanes, *Synth. Commun* 1998, 28, 4531. Ballini R; Marcantoni E; Petrini M Synthesis of

- functionalized nitroalkanes by oxidation of oximes with urea-hydrogen peroxide complex and trifluoroacetic anhydride, *Tetrahedron Lett* 1992, 33, 4835 Perborate: Manna MS; Mukherjee S Organocatalytic Enantioselective Formal C(sp²)-H Alkylation, *J. Am. Chem. Soc* 2015, 137, 130 Hydrogen peroxide: [PubMed: 25551319] Cardona F; Soldaini G; Goti A Methyltrioxorhenium-Catalyzed Oxidation of Aromatic Aldoximes, *Synlett*, 2004, 9, 1553 Molybdenum salts: Ballistreri FP; Barbuzzi E; Tomaselli GA; Toscano RM Useful Oxidation Procedure of Oximes to Nitro Compounds with Benz-Mo in Acetonitrile, *Synlett*, 1996, 1093.
18. Vineyard MK; Molson RL; Budde FE; Walton JR Continuous process for on-site and on-demand production of aqueous peracetic acid. U.S. Patent 7,012,154, Mar. 14, 2006.
19. (a) Murphy A; Pace A; Stack TDP Ligand and pH Influence on Manganese-Mediated Peracetic Acid Epoxidation of Terminal Olefins, *Org. Lett* 2004, 6, 3119. [PubMed: 15330602] (b) Lokkesmoe KD; Oakes TR Peroxy acid generator. U.S. Patent 5,122,538, Jun. 16, 1992.
20. see supporting information for more details.
21. Wang Y-W; Liao M-S; Shu C-M Thermal hazards of a green antimicrobial peracetic acid combining DSC calorimeter with thermal analysis equations, *Journal of Thermal Analysis and Calorimetry* 2015, 119, 2257.
22. Stoessel F Thermal Safety of Chemical Processes WILEY-VCH Verlag GmbH & Co KGaA: Weinheim, 2008, Chapter 3, pp. 68.
23. Schmidt C; Senon AH The Thermal Decomposition of Peracetic Acid in the Vapor Phase, *Can. J. Chem* 1963, 41, 1819.
24. White TD; Alt CA; Cole KP; Groh JM; Johnson MD; Miller RD How to Convert a Walk-in Hood into a Manufacturing Facility: Demonstration of a Continuous, High-Temperature Cyclization to Process Solids in Flow, *Org. Process Res. Dev* 2014, 18, 1482. See supporting information for details.
25. Abrams ML; Buser JY; Calvin JR; Johnson MD; Jones BR; Lambertus GR; Landis CR; Martinelli JR; May SA; McFarland AD; Stout JR Continuous Liquid Vapor Reactions Part 2: Asymmetric Hydroformylation with Rhodium-Bisdiazaphos Catalysts in a Vertical Pipes-in-Series Reactor, *Org. Process Res. Dev* 2016, 20, 901.
26. (a) Johnson MD; May SA; Calvin JR; Lambertus GR; Kokitkar PB; Landis CR; Jones BR; Abrams ML; Stout JR Continuous Liquid Vapor Reactions Part 1: Design and Characterization of a Reactor for Asymmetric Hydroformylation, *Org. Process Res. Dev* 2016, 20, 888–900. (b) Johnson MD; May SA; Haeberle B; Lambertus GR; Pulley SR; Stout JR Design and Comparison of Tubular and Pipes-in-Series Continuous Reactors for Direct Asymmetric Reductive Amination, *Org. Process Res. Dev* 2016, 20, 1305.
27. (a) Gutmann B; Elsner P; Glasnov T; Roberge DM; Kappe CO Shifting Chemical Equilibria in Flow—Efficient Decarbonylation Driven by Annular Flow Regimes, *Angew. Chem Int. Ed* 2014, 53, 11557. [PubMed: 25196172] (b) Sebastien Monfette S; Markus Eyholzer M; Dominique M. Roberge DM; Fogg DE Getting Ring-Closing Metathesis off the Bench: Reaction-Reactor Matching Transforms Metathesis Efficiency in the Assembly of Large Rings, *Chem. Eur. J* 2010, 16, 11720. [PubMed: 20821763]
28. Vara B; Mayasundari A; Tellis J; Danneman M; Arredondo V; Davis T; Min J; Finch K; Guy RK; Johnston JN Organocatalytic, Diastereo- and Enantioselective Synthesis of Nonsymmetric *cis*-Stilbene Diamines: A Platform for the Preparation of Single Enantiomer *cis*-Imidazolines for Protein-Protein Inhibition. *J. Org. Chem* 2014, 79, 6913. [PubMed: 25017623]

Figure 1.
Stoessel diagram for oxime oxidation by peracetic acid

Figure 2.
Major drivers for continuous platform development

Scheme 1.
Methods for nitroalkane synthesis

Scheme 2.
Technological scheme of the continuous process

Scheme 3.
aza-Henry reaction of the continuously generated nitroalkane

Table 1.

Substrate evaluation for the oxime oxidation with peracetic acid (traditional batch preparation)

entry	R ₁	R ₂	conditions	yield	sm	acid	entry	R ₁	R ₂	conditions	yield	sm	acid
1		H	C	34%	-	29%	9		H	B	66%	8%	7%
2		H	A	52%	-	31%	10		H	D	49%	33%	5%
3		H	A	38%	15%	19%	11		H	B	37%	14%	9%
4		H	A	43%	19%	8%	12		H	B	32%	8%	-

entry	R ₁	R ₂	conditions	yield	sm	acid	entry	R ₁	R ₂	conditions	yield	sm	acid
5		H	C	32%	14%	24%	13		H	B	<5%	-	-
6		H	B	40%	-	18%	14		H	B	<15%	-	13%
7		H	B	31%	-	27%	15			B	56%	6%	-
8			D	21%	-	-	16			B	49%	-	-

^aConditions: All reactions employed 20 mmol nitroalkane in 7 mL of AcOH (2.86 M) warmed to 92 °C, 15–16 % wt AcOOH was added dropwise maintaining temperatures in 90–97 °C range. Conditions A: 4.0 equiv of AcOOH over 30 min with 50 min overall reaction time. Conditions B: 2.0 equiv of AcOOH over 20 min with 30 min reaction time. Conditions C: 4.0 equiv of AcOOH over 30 min with 40 min reaction time. Conditions D: 1.2 equiv of AcOOH over 10 min with 15 min reaction time. Conditions E: 1.05 equiv of AcOOH over 9 min with 10 min reaction time.

Table 2.

Oxime oxidation using different platforms

Entry	Reactor type	conditions	nitroalkane ^b	starting material ^b	benzoic acid ^b	yield (isolated) ^a
1.	batch: open flask (0.5M)	90–96 °C, 20 min	83%	2%	15%	52%
2.	stainless steel	90 °C, 20 min	11%	-	63%	
3.	PFR (2.5 mL)	80 °C, 3 min	8%	37%	55%	
4.	PFA PFR (2.5 mL)	95 °C, 20 min	34%	15%	47%	
5.	port connector ²⁴	95 °C, 15 min	25%	-	63%	
6.	PFA pipes-in-series (12 mL)	90 °C, 35 min	69%	7%	24%	52%
7.	PFA pipes-in-series (12 mL)	95 °C, 40 min	69%	3%	28%	
8.	PFA pipes-in-series (2x AcOOH split, 12 mL)	95 °C, 35 min	75%	6%	19%	54%
9.	PFA pipes-in-series (4x AcOOH split, 12 mL)	95 °C, 40 min	81%	2%	16%	62%
10.	PFA pipes-in-series (4x AcOOH split, 42 mL)	87–89 °C, 33 min	81%	7%	12%	
11.	PFA pipes-in-series (1×60%, 3×13.3 AcOOH split, 42 mL)	87–89 °C, 33 min	82–84.5%	3–5%	12–13%	

^aYields were determined based on material isolated after batch extraction and flash column chromatography (silica gel, 0–4% heptane/EtOAc).

^bRatio of nitroalkane, oxime and benzoic acid (as the percent of the sum) were determined based on NMR analysis of the crude reaction mixture.