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Scalable On-Demand Production of Purified Diazomethane Suitable for Sensitive Catalytic Reactions

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ABSTRACT: We have developed a convenient development-scale reactor (0.44 mol/h) to prepare diazomethane from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) in ∼80% yield. Diazomethane (CH_2N_2) made with this reactor is extracted into nitrogen gas from the liquid reaction mixture, effectively removing it from reagents and byproducts that may interfere in subsequent reactions. Vertically oriented tubular reactors were used to produce and consume diazomethane in situ. Key features of this reactor include high productivity and correspondingly low reactor volume (reactor volume/liquid flow rate = 6.5 min) and a commercially available gas/liquid separator equipped with a selectively permeating hydrophilic membrane. The design of the reactor keeps the inventory below 53 mg of CH_2N_2 during normal operation. The reactor was demonstrated by generating CH_2N_2 that was used in a connected continuous reactor. We evaluated esterification reactions and a continuous Pd-catalyzed cyclopropanation reaction with the reactor and achieved high conversion with 1.5 and 4.1 equiv of MNTS precursor, respectively.

KEYWORDS: *Diazomethane, cyclopropanation, plug flow reactor, continuous manufacturing*

INTRODUCTION

Diazomethane (CH_2N_2) is a powerful synthetic reagent, but it is rarely used beyond the laboratory scale because it is toxic, explosive, and a gas under ambient conditions (bp = −23 °C).[1] Continuous flow technology can be used to simultaneously produce and consume hazardous reagents, mitigating the risks associated with larger quantities of these materials that would be necessary in a batch process. This opportunity has drawn several academic and industrial groups to develop continuous processes for preparing diazomethane.[2] In order to prepare a complex intermediate needed to prepare an investigational drug, we were interested in developing an approach to prepare diazomethane suitable for a palladium-catalyzed cyclopropanation reaction.[3] After a range of cyclopropanation conditions were tested for this compound, the palladium-catalyzed conditions using diazomethane proved the most promising. This approach to cyclopropanation has been noted in the literature to provide a good complement to the more commonly used Simmons−Smith conditions.[4]

One significant challenge is purification of diazomethane to meet the requirements of downstream chemistry. The harsh conditions of diazomethane synthesis (basic and oxidizing) mean that a workup or purification is typically needed before using the CH_2N_2 reagent.[5] The traditional lab-scale method for purification of diazomethane is codistillation with diethyl ether.[6] This approach has been practiced by hazardous chemistry specialists to prepare multikilogram quantities of diazomethane, but the operations were performed under remote control behind explosion-proof barriers, capabilities that are not widely available in the pharmaceutical industry.[7]

Liquid−liquid extraction is another simple method to prepare organic solutions of CH_2N_2, and it has been applied to continuous processes including at the kilogram scale.[8] A drawback of liquid−liquid extraction is that undesirable impurities (e.g., base, unreacted *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) could contaminate the organic phase and poison downstream catalytic reactions. In the palladium-catalyzed cyclopropanation reaction of interest, we found that diazomethane prepared by liquid−liquid extraction did not lead to appreciable levels of conversion, whereas diazomethane purified by codistillation with diethyl ether gave nearly complete conversion. For that reason, we sought to develop a diazomethane synthesis strategy based on gas extraction and gas/liquid-phase separation that would be convenient for process development and kilo-lab deliverables.

In addition to the distillation process described above, there are two other known strategies to purify diazomethane by taking advantage of the high vapor pressure and low molecular weight of CH_2N_2. Gas-permeable tubing has successfully been demonstrated to allow diazomethane to diffuse into another solution while leaving behind undesired byproducts.[9] This approach has been used to generate CH_2N_2 suitable for palladium-catalyzed cyclopropanation reactions.[10] Although

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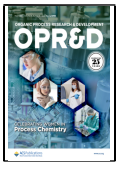

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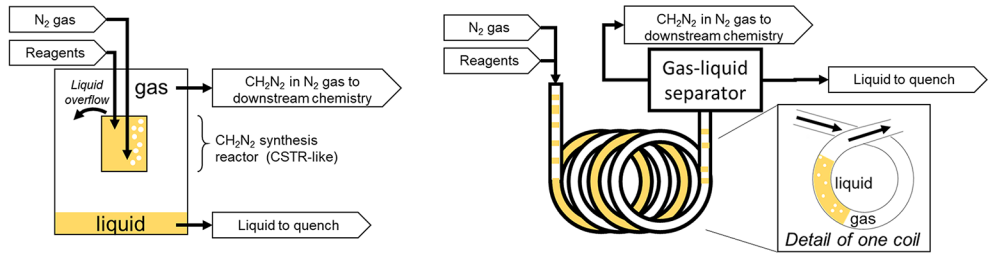


Figure 1. Design of previously reported CSTR-type reactors for CH_2N_2 synthesis and extraction into nitrogen gas (left) compared with the plug flow reactor (PFR)-type design that is the subject of this article (right). In the PFR design, the tubing diameter is large enough to allow the gas to bypass the liquid, allowing it to experience a shorter residence time in the reactor.

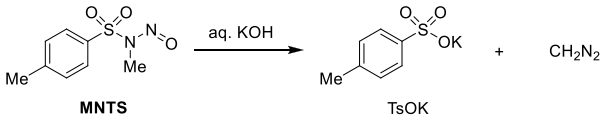
this approach is appealing, the tubing needed is not widely available. To the best of our knowledge, this concept has not been extended beyond a laboratory demonstration.

Two examples of diazomethane synthesis that are reported on a kilogram scale and beyond use an approach similar to codistillation, but instead of using solvent vapor to carry the diazomethane away from the preparation reaction mixture, the diazomethane is extracted using a nitrogen sweep or sparge.[11,12] This approach can be performed using nonflammable solvents such as DMSO, and the nitrogen flow rate can be selected to keep the diazomethane headspace concentration below the lower explosive limit (LEL). In both cases, the reagents needed to prepare CH_2N_2 are mixed in an overflowing vessel analogous to a continuous stirred tank reactor (CSTR) enclosed within a larger vessel that is purged with nitrogen (Figure 1). In one case, the large volume of the reactor required the authors to perform a test to ensure that a detonation within the reactor would not cause it to rupture.

Whereas the approach of gas−liquid extraction is attractive because it allows access to high-quality diazomethane while also avoiding the use of flammable solvents, the previously reported reactor designs had a large headspace volume. Minimizing headspace is a guiding principle for designing systems with hazardous gaseous reagents, as a smaller headspace will reduce the consequences in the event of a violent decomposition of diazomethane. Herein, we present a scalable reactor design to continuously produce and consume diazomethane suitable for metal-catalyzed cyclopropanation reactions. This reactor is based on a tubular reactor design that provides safety advantages over the CSTR designs previously reported (Figure 1), chiefly by operating with a much smaller headspace volume.

RESULTS AND DISCUSSION

Choice of Reagents and Solvent. Diazomethane can be synthesized from several precursors, but *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) is attractive for gas-phase extraction of CH_2N_2 due to its low vapor pressure (eq 1).[1b]



(1)

MNTS is also significantly less toxic than alternative precursors derived from urea and guanidine.[13] Given the concerns of handling these materials and introducing trace quantities of toxic *N*-nitroso compounds into the product of the reaction, we opted to use MNTS for our process. Anhydrous MNTS suffers from thermal instability and can only be shipped in small quantities due to its low self-accelerating decomposition temperature, but it has been determined that bulk quantities up to 50 kg can be safely handled and stored by preparing MNTS wetted with 10−15% w/w water.[11]

A high-boiling solvent is required to avoid solvent evaporation during the process of extracting diazomethane into the gas phase from the aqueous/organic solvent system. Though we drew inspiration from the DMSO solvent system reported by Proctor and Warr,[11] we elected to use sulfolane in place of DMSO to avoid thermal instability issues that have been recently reported in the literature.[14] Various compositions of sulfolane/H_2O were examined, aiming for high solubility and stability of MNTS in solution. The 95:5 (w/w) mixture of sulfolane and H_2O, a liquid at room temperature, is a suitable solvent for MNTS at concentrations up to 20% w/w and is stable up to 4 days when stored as a solution at 2−8 °C without appreciable decomposition of the reagent by high-performance liquid chromatography (HPLC) or ^{1}H NMR spectroscopy. Compared to the process reported by Proctor and Warr, we also increased the concentration of the KOH solution to reduce the amount of water in the reaction mixture. This change made the process less prone to crystallization in the reactor, a major challenge in earlier work with diazomethane synthesis performed in our laboratories.

Reactor Design. Our reactor design is based on a coil of relatively large diameter (1/4 in. i.d.; 3/8 in. o.d.) PFA tubing oriented so that the axis of the coil is parallel to the ground, like a wheel (Figure 2). This configuration allows for a gas to advance through the reactor more quickly than the liquid by bubbling through liquid-phase slugs at the bottom of the coil. In one reported example, the liquid residence time was 3 times longer than the corresponding gas phase (4 h for the liquid phase versus 1.3 h for gas phase).[15] We reasoned that this effect would be beneficial for diazomethane synthesis because a longer liquid residence time would allow more time for MNTS to react, whereas a short gas residence time would allow the unstable CH_2N_2 product to be removed from the reactor quickly, minimizing decomposition. In our process, nitrogen was used to extract the gaseous diazomethane from the liquid medium. We took advantage of the same vertical tubing coil reactor design for the downstream chemistry, which requires the CH_2N_2 to be extracted from the gas phase into the liquid phase. Photographs of the two reactors are shown in the Supporting Information.

The reactor mixes the liquid reaction mixture with a nitrogen carrier gas that serves three purposes. First, the carrier

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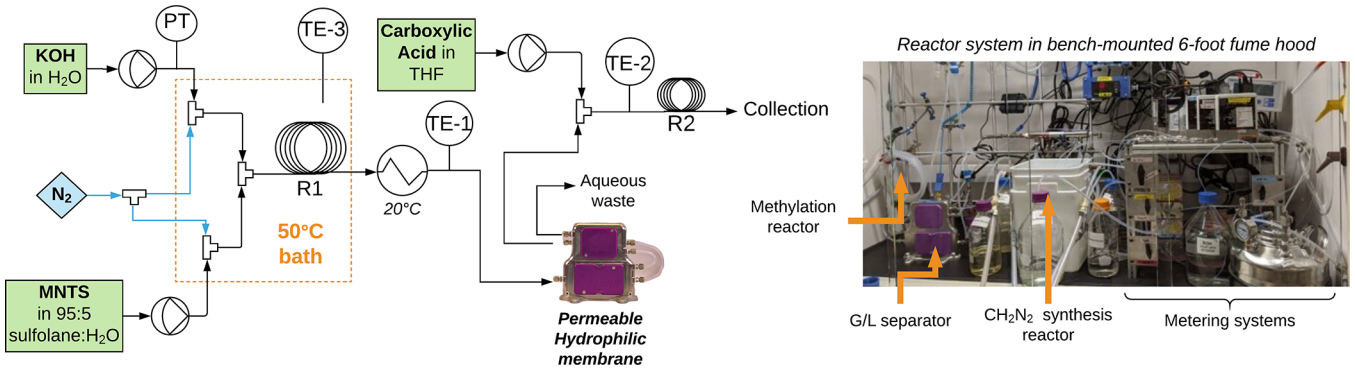

Figure 2. Process flow diagram of diazomethane synthesis reactor and downstream carboxylic acid methylation. *R*1 = 240 mL, *R*2 = 120 mL. Feed rates: KOH in H_2O (13.7% w/w), 4.11 g/min; MNTS in 95:5 sulfolane/H_2O (12.3% w/w), 14.6 g/min; N_2, 1.02 slpm per feed (2.04 slpm total); carboxylic acid in THF (0.5 mmol/g solution), 8.34 g/min.

Table 1. Summarized Results from Diazomethane Generation System Using Zaiput SEP-200 with 1.52 equiv of KOH and 1.5 equiv of Benzoic Acid (0.5 M)

			flow rates in diazomethane generator		
entry	MNTS throughput (mmol/min)	solvent	liquid (g/min)	N_2 (slpm)	yield (%) of CH_2N_2
1	4.9	DMSO/DGME[a]/H_2O	7.4	0.685	75–80
2	4.9	sulfolane/H_2O	12.0	1.07	76–82
3	9.6	sulfolane/H_2O	24.0	2.13	77–79
4	13.7	sulfolane/H_2O	33.7	2.99	64
5	19.6	sulfolane/H_2O	47.7	4.27	incomplete gas–liquid separation

[a]DGME = diethylene glycol monoethyl ether.

gas extracts CH_2N_2 from the reaction mixture and acts as a solvent to carry it into downstream processes. Second, the carrier gas prevents the gas-phase concentration of CH_2N_2 from reaching levels that could lead to an explosion. Finally, the nitrogen carrier gas is also used to prevent liquid reagent feeds from migrating back up the other reagent's dosing line, which causes precipitation. The nitrogen feed is split so that half was introduced with the KOH feed, while the other half was introduced with the MNTS feed to protect both feed lines from blockage (Figure 2).

The flow rate of nitrogen gas was selected to prevent the gas-phase concentration of CH_2N_2 from exceeding the LEL, which has been established to be ~15% v/v in nitrogen gas.[11] To provide a margin of safety, we designed our total nitrogen flow rate to keep the CH_2N_2 concentration below 50% of the LEL. For conditions with 9.6 mmol/min MNTS throughput, we used a total nitrogen flow rate of 3.0 slpm (standard liters per minute), which would result in a CH_2N_2 concentration of less than 48% of the LEL, the exact concentration depending on the yield of CH_2N_2 in the generator.

To separate the CH_2N_2-containing gas phase from the liquid phase, we evaluated two approaches for a gas–liquid separator. The first was a small glass pressure-rated vessel. We allowed liquid to accumulate in the vessel and then drained it periodically. While this was effective to establish a proof of concept, the headspace in that vessel posed a risk of explosion; the mechanical valves used can trap unstable reaction mixture in the valve body when closed, and the periodic draining introduces additional operational complexity. We opted to replace that system with a commercially available gas–liquid separator based on selective wetting of a membrane (Zaiput SEP-200, Figure 2). By comparison, this piece of equipment has no moving parts and a much smaller overall volume (35 mL). The separator was fitted with a hydrophilic PTFE membrane, which causes the liquid phase to permeate the membrane while the gas phase is retained. The overall reactor volume including the downstream reactor for cyclopropanation is 515 mL; therefore, during normal operation, the total inventory of CH_2N_2 is expected to be less than 29 mL_N (volume at 1 bar pressure and 273 K) or 1.3 mmol (53 mg).

Demonstration of the Diazomethane Synthesis Reactor System. Having established our reactor design, a downstream reaction was introduced to the system to evaluate the yield and productivity of CH_2N_2. To establish the limiting throughput of the reactor system, we performed a series of experiments increasing the MNTS feed rate given in Table 1. The gas stream containing CH_2N_2 was mixed with a solution containing an excess of benzoic acid. These reactions were run at incomplete conversion of benzoic acid to ensure high conversion of diazomethane. The yield of methyl benzoate was used to establish the productivity of the diazomethane synthesis reaction. Overall, the platform was able to consume 9.6 mmol/min of MNTS while maintaining a diazomethane yield of 75–80% (Table 1, entry 3). At higher throughput, we observed some liquid in the retentate stream of the separator. Larger gas–liquid separators based on the same design are commercially available, and they would allow access to faster flow rates and therefore greater throughput.

To establish the utility of the reactor system, we performed a second set of experiments under preparative conditions with an excess of MNTS (and therefore CH_2N_2) compared to the carboxylic acid substrate. Results were analyzed with a calibrated HPLC method. From the results in Table 2, it is apparent that the reactor uses the diazomethane very efficiently, requiring only a slight excess of diazomethane to reach high yields of the ester product.

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Table 2. Diazomethane Stoichiometry Studies for the Methylation of Benzoic Acid (Performed at MNTS throughput of 6.6 mmol/min)

entry	equiv of MNTS	equiv of CH_2N_2[a]	yield (%)
1	1.00	0.75−0.80	82
2	1.25	0.94−1.00	100
3	1.50	1.13−1.20	99

[a]Based on 75−80% yield from MNTS.

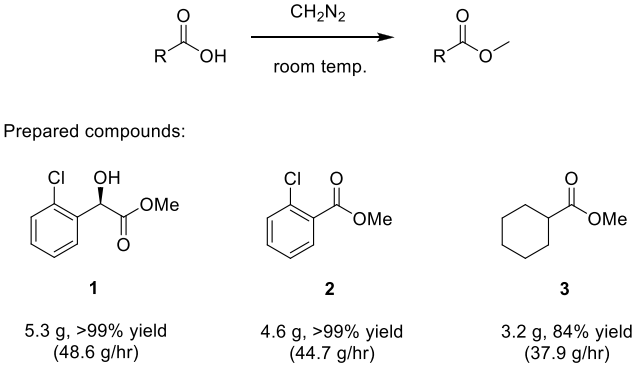
Table 3. Summary of Results from the Cyclopropanation Using Styrene with a MNTS throughput of 9.7 mmol/min with 2 mol % of $Pd(OAc)_2$ with Regard to Styrene

entry	styrene throughput (mmol/min)	MNTS equiv relative to styrene	molar conversion[a] (%)
1	2.38	4.1	99
2	3.56	2.7	84

[a]Defined as [product]/([starting material] + [product]).

Having established that these methylation reactions can be performed at very low excess of diazomethane, we extended the conditions to three additional carboxylic acids (Scheme 1)

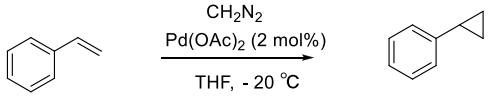
Scheme 1. Methylation of Carboxylic Acids



using 1.5 equiv of MNTS. Compound **1** is an important intermediate in the synthesis of clopidogrel, an antiplatelet medication on the World Health's Organization List of Essential Medicines. All reactions reached full conversion from the respective carboxylic acids, and **1** and **2** and were isolated in greater than 99% yield. Compound **3** had a lower isolated yield possibly due to evaporation during isolation.[16]

The stability of this methylation process using benzoic acid was tested over 5.5 h of continuous operation. The conversion of benzoic acid to methyl benzoate was periodically monitored by HPLC during the run shown in Figure 3. Throughout the duration of the reaction, all feed flows were steadily delivered and no rise in pressure was observed.

Once the efficiency and stability of the diazomethane generation reaction were established, we investigated the reaction of interest, palladium-catalyzed cyclopropanation (Figure 4).



We repeated the diazomethane synthesis at the highest flow rate (9.6 mmol/min) and designed the reaction to have 2.7 or 4.1 equiv of MNTS with respect to styrene (Table 3). With 4.1

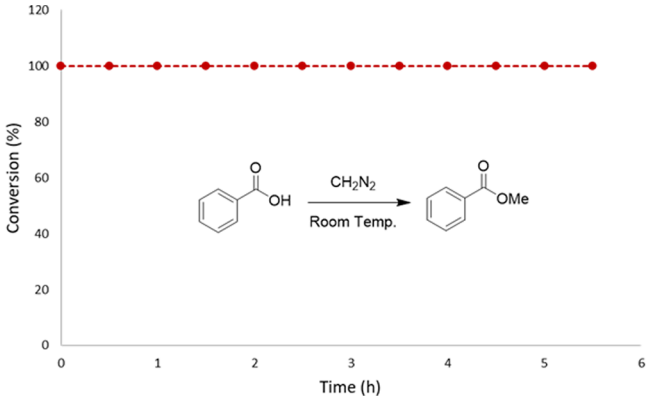


Figure 3. System stability of benzoic acid esterification with diazomethane over 5.5 h. Conversion was monitored by HPLC at each 0.5 h data point.

equiv of MNTS, 99% molar conversion was achieved, indicating that the purification strategy was sufficient for this metal-catalyzed reaction. The results are reported in molar conversion, which was calculated with a calibrated HPLC method. While we observed high conversion in these reactions, the cyclopropanation reactor gradually became fouled with black solids near the catalyst addition point (presumed to be palladium black) and white solids elsewhere in the cyclopropanation reactor (presumed to be hydrocarbon polymer formed from diazomethane). Whereas this fouling appears downstream of the sensitive gas−liquid separator, managing reactor fouling will be an important consideration for extended operation of this process.

CONCLUSION

We have developed a small-footprint, on-demand CH_2N_2 generation system that is robust and able to support development lab activities and early material deliveries with a diazomethane generation rate of 0.44 mol/h. The key reactor technology used is scalable, with a straightforward path to 10× scale (~4−5 mol/h) with commercially available equipment that does not rely on specialized materials such as gas-permeable tubing. At that scale, CH_2N_2 inventory would remain below 1 g, and the throughput could support small-volume manufacturing. This approach highlights the advantages of using continuous manufacturing to prepare hazardous reagents. By removing the constraints of only working with materials that are safe to use in large batch reactors, it may be possible to identify more direct synthetic routes to compounds of interest.

EXPERIMENTAL SECTION

WARNING! Diazomethane is extremely toxic and explosive. Any operations involving diazomethane should undergo a detailed process hazard assessment. Care should also be taken when handling MNTS, as *N*-methyl-*N*-nitroso compounds are known to be toxic, as well. MNTS-contaminated waste should be separated from other waste streams to prevent formation of diazomethane in waste containers.

General Materials and Methods. ^{1}H NMR spectra were recorded on a Varian 300 MHz instrument. 1,3,5-Trimethoxybenzene (Sigma-Aldrich, QNMR grade provided with traceable potency documentation) internal standard was used for quantification. Analytical HPLC analysis was carried out

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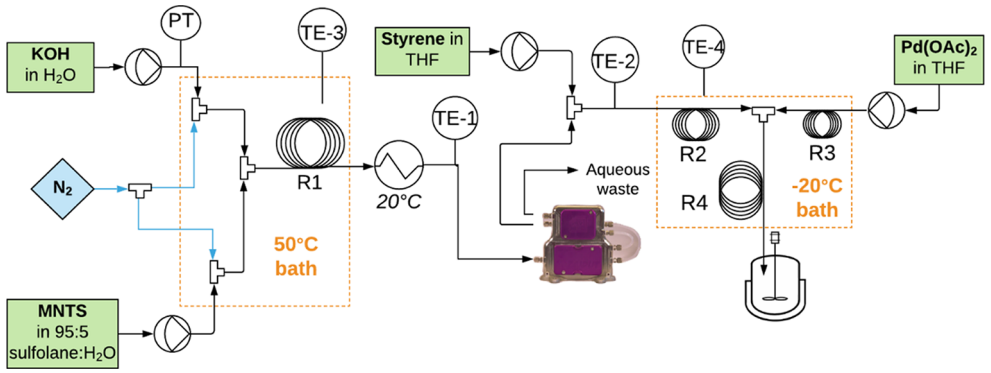

Figure 4. Process flow diagram of the cyclopropanation reactor. *R*1 = 240 mL, *R*2 = 120 mL, *R*3 = 0.5 mL, *R*4 = 120 mL. Flow rates: MNTS (10% w/w in 95:5 sulfolane/water), 20.7 g/min; KOH (25% w/w in water), 1.26 g/min; styrene (1.24% w/w in THF), 20−30 g/min; $Pd(OAc)_2$ (0.91% w/w in THF), 1.2−1.8 g/min.

Table 4. Reactor Specifications Used in Methylation or Cyclopropanation

reactor	ID	volume (mL)	tubing type
CH_2N_2 generation reactor	*R*1	240	PFA 3/8 in. o.d.; 1/4 in. i.d.
dissolution of diazomethane	*R*2	120	PFA 3/8 in. o.d.; 1/4 in. i.d.
precooling coil for $Pd(OAc)_2$ catalyst (only used for cyclopropanation reaction)	*R*3	0.5	PFA 1/16 in. o.d.; 1/32 in. i.d.
cyclopropanation or methylation reactor	*R*4	120	PFA 3/8 in. o.d.; 0.25 in. i.d.

according to a method provided in the Supporting Information.

All chemicals were purchased from commercial suppliers and used as received unless otherwise noted: KOH (BDH Chemicals), benzoic acid (Sigma-Aldrich), tetrahydrofuran stabilized with BHT (Oakwood Chemicals), methyl benzoate (Sigma-Aldrich), 2-chloromandelic acid (Sigma-Aldrich, 94.5% w/w), 2-chlorobenzoic acid (Sigma-Aldrich), cyclohexanecarboxylic acid (Sigma-Aldrich), styrene (Sigma-Aldrich), $Pd(OAc)_2$ (Oakwood Chemicals), sulfolane (Oakwood Chemicals). MNTS was synthesized following a published procedure.[17]

Reactor Configuration. Solutions of KOH, benzoic acid, $Pd(OAc)_2$, styrene, and 95:5 w/w sulfolane/H_2O were delivered to the reactor through dual diaphragm pumps, and the flow rates were controlled by feedback control with Coriolis mass flow meters. MNTS solution in 95:5 w/w sulfolane/H_2O was delivered from a pressurized vessel using a metering valve that was controlled by feedback with a Coriolis mass flow meter. Nitrogen dosing was controlled by thermal gas mass flow meters. The Zaiput SEP-200 gas−liquid separator was fitted with an IL-2000 hydrophilic PTFE membrane (pore size 1 μm).

The tubing reactors were constructed of 3/8 in. o.d., 1/4 in. i.d. PFA tubing, except for the catalyst precooling coil, which was 1/16 in. o.d. and 1/32 in. i.d. The reactors and their dimensions are found in Table 4. The catalyst precooling coil and cyclopropanation reactor were not used in the methylation reactions; the reaction was completed in the dissolution coil.

Palladium-Catalyzed Cyclopropanation. MNTS (237 g; 80.7% w/w potency) was dissolved in 80:20 w/w sulfolane/H_2O (1.67 kg) to give a 10% w/w yellow solution. Sonication was required to fully dissolve the MNTS. KOH (255 g) was dissolved in 764 g of water. Styrene (108 g) was dissolved in 8.61 kg of THF to give a 1.24% w/w solution. $Pd(OAc)_2$ (0.65 g) was dissolved in 71 g of THF and then filtered through a disposable filter under nitrogen to give a light red/orange-colored 0.91% w/w solution.

The metering system was designed to facilitate two stoichiometries of MNTS (Table 5).

We started the process using the conditions for 4.1 equiv of MNTS. The reactor effluent was diverted to a quench vessel charged with acetic acid for 6 min followed by product collection. The crude product stream was collected for 2 min and analyzed on a calibrated HPLC method to give molar conversion of the reaction (99% molar conversion). The metering system was reconfigured to deliver the conditions for 2.7 equiv of MNTS by increasing the flow rates for the styrene and $Pd(OAc)_2$ solutions. After the flow rates stabilized, the reactor effluent was diverted to a quench vessel charged with acetic acid for 6 min followed by product collection. The crude product stream was collected for 2 min and analyzed on a calibrated HPLC method to give molar conversion of the reaction (84% molar conversion).

Table 5. Operating Conditions for the Cyclopropanation Process

	4.1 equiv of MNTS		2.7 equiv of MNTS	
feed stream	flow rate	throughput (mmol/min)	flow rate	throughput (mmol/min)
10.0% w/w MNTS	20.7 g/min	9.7	20.7 g/min	9.7
25.0% w/w KOH(aq)	1.26 g/min	1.52	1.26 g/min	1.52
nitrogen gas	3120 sccm	29	3120 sccm	29
1.24% w/w styrene in THF	19.87 g/min	2.38	29.67 g/min	3.56
0.91% w/w $Pd(OAc)_2$ in THF	1.18 g/min	0.05	1.76 g/min	0.07

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00485.

Procedure for carboxylic acid methylation, HPLC method (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Eric N. Jacobsen on the occasion of his 60th birthday.

■ ABBREVIATIONS

CSTR, continuous stirred tank reactor; in., inch; LEL, lower explosive limit; MNTS, *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide; PFA, perfluoroalkoxy alkane; PFR, plug flow reactor; PT, pressure transmitter; PTFE, polytetrafluoroethylene; slpm, standard liters per minute (gas flow); TE, temperature element

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