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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

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Supporting Information

ABSTRACT: Herein, we describe the use of continuous flow chemistry for selective, efficient and reproducible nitration of 2-isopropoxybenzaldehyde to produce the desired 2-isopropoxy-5-nitrobenzaldehyde, an important building block in the preparation of a ligand of nitro-substituted Hoveyda–Grubbs metathesis catalyst. Nitration was done with red fuming HNO_3, and this challenging and hazardous process was performed using a flow-through silicon-glass microreactor equipped with a set of temperature sensors, and with a productivity of 13 g/h, providing us with a reproducible chemical process amenable for production of sufficient quantities of 2-isopropoxy-5-nitrobenzaldehyde for ongoing large-scale synthesis of nitro-substituted Hoveyda–Grubbs metathesis catalyst.

INTRODUCTION

Olefin metathesis is a powerful transformation that is widely used in organic synthesis for the formation of carbon–carbon double bonds.[1−3] The importance of metathesis in the chemical field was recognized by the Nobel Prize in Chemistry awarded to Yves Chauvin, Richard R. Schrock, and Robert H. Grubbs in 2005.[4] The development of new metathesis catalysts that are stable, air- and moisture resistant, and highly active is the major factor contributing to the continuing success of this transformation (Figure 1).

For current applications, commercially available first- and second-generation catalysts **G1** and **G2** are already remarkably efficient in terms of activity, selectivity, and functional group tolerance (Figure 1).[1] The catalyst **H1**, introduced by Hoveyda et al.,[5] and its second-generation congener **H2**, possesses reactivity comparable to that of **G2** and are efficient for metathesis of highly electron-deficient substrates (e.g., acrylonitrile) and in addition gives the possibility of a catalyst reuse or immobilization.[6,7] Grela introduced an electron-withdrawing nitro group on the aromatic ring in the parent **H2** catalyst. This resulted in the discovery of *nitro*-substituted Hoveyda–Grubbs catalyst **N2**, that even surpasses the initiation rate of the parent **H2**.[8] So far, the **N2** has shown impressive activity in various ring-closing, cross and enyne metathesis reactions.[8] Additionally **N2** found applications in material science e.g. in ring-opening cross metathesis polymerisation[9a] and acyclic diene metathesis polymerization of 1,4-divinyl-benzenes[9b] as well as in numerous total syntheses of natural and biologically active compounds e.g. (−)-securinine,[9c] precursor of hexacyclinic acid,[9d] (+)-ricciocarpin A,[9e] viridiofungin A derivative,[9f] the first reported hepatitis C virus (HCV) NS3 protease inhibitor (BILN 2061),[9g,h] largazole,[9i] FR901464,[9j] and cathepsin K inhibitor.[9k] In order to further increase the number of applications of **N2**, especially in the industry, a simple, repeatable, and high-yielding large-scale process for the synthesis of this catalyst as well as key intermediates needed for its construction is required. Herein, we report on the convenient large-scale synthesis of 2-isopropoxy-5-nitrobenzaldehyde, an important building block in the preparation of **N2**. The described protocol involves the use of a continuous flow reactor for conducting the nitration process.

RESULTS AND DISCUSSION

Up to date the most convenient large-scale protocol for the synthesis of **N2** was reported by Grela and co-workers and involved reacting **H2** with isopropoxy-4-nitro-2-[(*E*,*Z*)-1-propenyl]benzene (**1**) in the ligand exchange process (Scheme 1).[10]

The synthesis of isopropoxy-4-nitro-2-[(*E*,*Z*)-1-propenyl]-benzene (**1**) is a three-step reaction sequence (Scheme 2). The methodology used by Grela[10] is presented as *Route A*, and the protocol used by us as *Route B*. Both *Route A* and *Route B* share the same third step, that is the Wittig reaction. They differ however, in the preparation of the substrate, 2-isopropoxy-5-nitrobenzaldehyde (**5**) (Scheme 2).

In our hands all attempts to reproduce the outcome of the nitration protocol reported by Grela failed (Scheme 2, *Route A*). In general, the selectivity of the reaction was poor, affording in the best case a mixture of **3** and its ortho isomer **6** in 60:40

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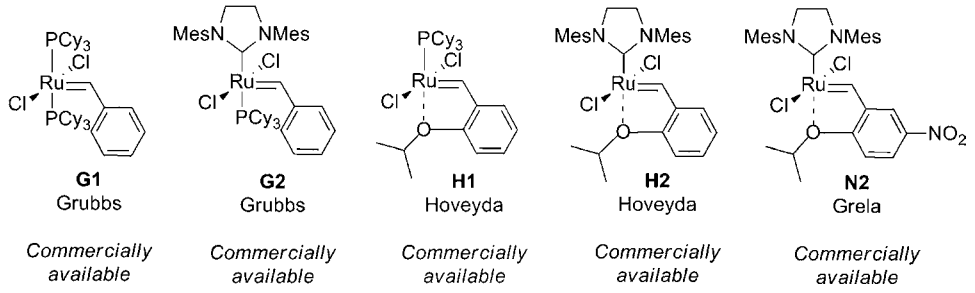
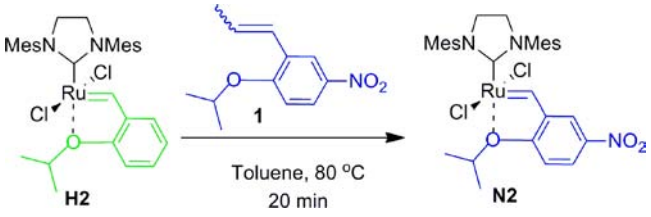


Figure 1. Selected modern and commercially available ruthenium-based catalysts for olefin metathesis. Cy = cyclohexyl, Mes = mesityl (1,3,5-trimethylphenyl).

Scheme 1. Large-scale preparation of N2: ligand exchange reported by Grela et al.[10]

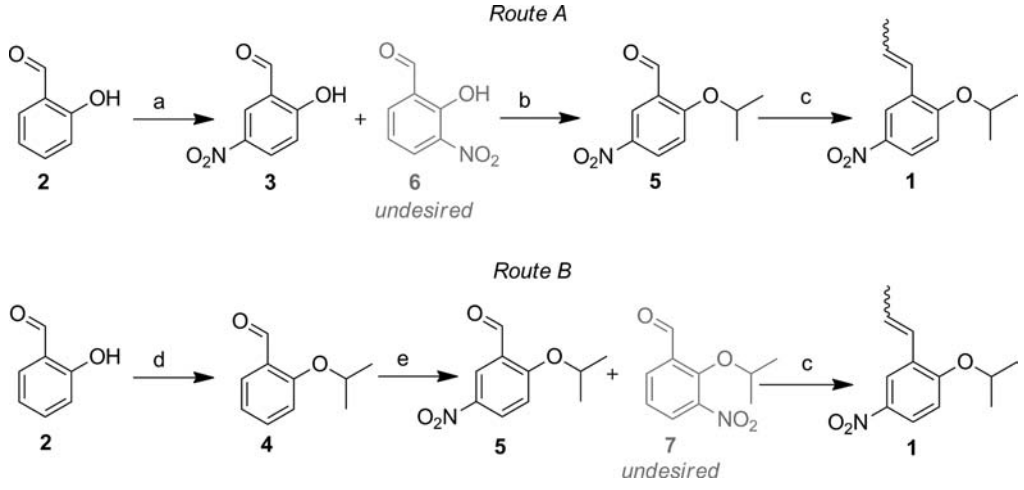


ratio. Isolation of **3** from such a mixture by, as reported by Grela, crystallization from 20% AcOH was found to be tedious and unproductive. These results prompted us to investigate other nitration protocols, and to our satisfaction, we discovered that the nitration process proceeds more selectively when 2-isopropoxybenzaldehyde (**4**) is used as substrate and nitration is carried out with the use of red fuming HNO_3 (Scheme 2, *Route B*). The improved selectivity observed in the case of **4** when compared with that of **2** can be due to the steric effect of the bulky isopropoxy group that shields the ortho position. In the optimized batch protocol, **4** in CH_2Cl_2 was added dropwise to neat, red fuming HNO_3 at −10 °C. The resulting mixture was stirred and slowly warmed to 10 °C over 10 h. The alkali workup followed by recrystallization of the crude product from ethanol yielded the desired 2-isopropoxy-5-nitrobenzaldehyde (**5**) (an average isomer ratio **5**:**7** was 75:25). This protocol worked well for up to 100 g (0.6 mol) of starting material **4**, affording the desired **5** in 50% yield (see Experimental Procedures).

When performing the reaction on 1 kg (6.0 mols) of **4** in a 10-L minipilot reactor however, we encountered severe problems due to low mixing efficiency and poor cooling performance due to the heat evolved from the exothermic nitration reaction, leading to the formation of "*hot spots*" and, as a further consequence, to a drastic drop in the process selectivity (more undesired ortho isomer **7** was formed: isomer ratio **5**:**7** was 60:40) as well as the occurrence of undesired side reactions by HNO_3 used in excess, e.g. oxidation of 2-isopropoxy-5-nitrobenzaldehyde (**5**) to the corresponding carboxylic acid. As a consequence, the desired nitration product **5** was usually isolated in only 30% yield after tedious purification from its unwanted ortho isomer and other side products (see Experimental Procedures). In addition to the aforementioned problems, working with substantial amounts of red fuming HNO_3, a highly corrosive and toxic mineral acid, requires implementation of special safety and security protocols that are costly and time consuming. In order to circumvent the aforementioned problems and find a reproducible chemical protocol amenable for production of sufficient quantities of 2-isopropoxy-5-nitrobenzaldehyde (**5**) for ongoing large-scale synthesis of nitro-substituted Hoveyda−Grubbs metathesis catalyst **N2**, we decided to adapt this nitration chemistry to continuous flow.

Continuous flow chemistry utilizing microreactors is known to offer excellent heat exchange and narrowly distributed, well-

Scheme 2. Synthesis of isopropoxy-4-nitro-2-[(*E*,*Z*)-1-propenyl]benzene (1) in batch[a]



[a]Reagents and conditions: *Route A*: (a) AcOH, 65% HNO_3 (47% calculated for **3**); (b) iPrI, K_2CO_3, Cs_2CO_3 (cat.) (98%); (c) $Ph_3P{=}CHCH_3$ (80%).[10] *Route B*: (d) iPrI, K_2CO_3, (95%); (e) red fuming HNO_3 (50% calculated for **5**); (f) $Ph_3P{=}CHCH_3$ (80%).

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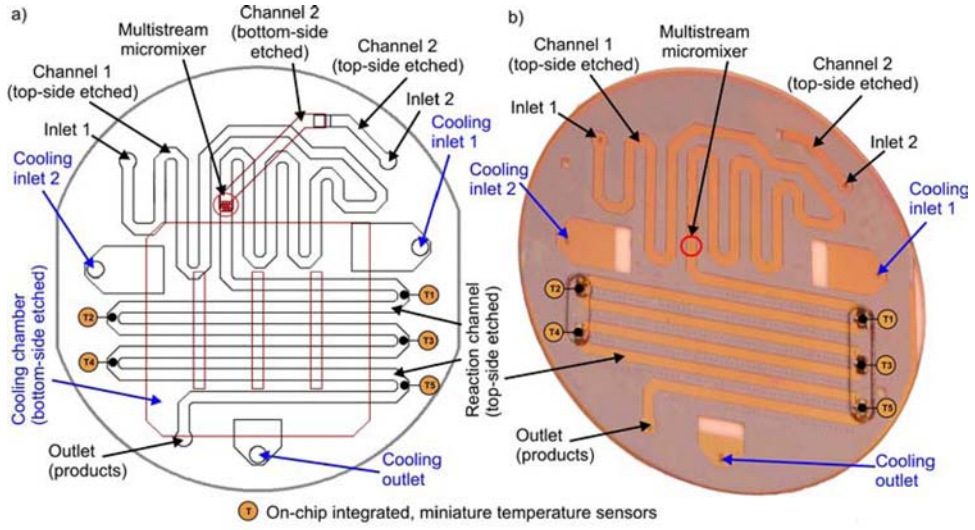

Figure 2. Three-inch wafer-scale, silicon–glass microreactor. (a) Topology of microchannels, localization of inlets, outlets, and temperature sensors. (b) Top view of fabricated device.

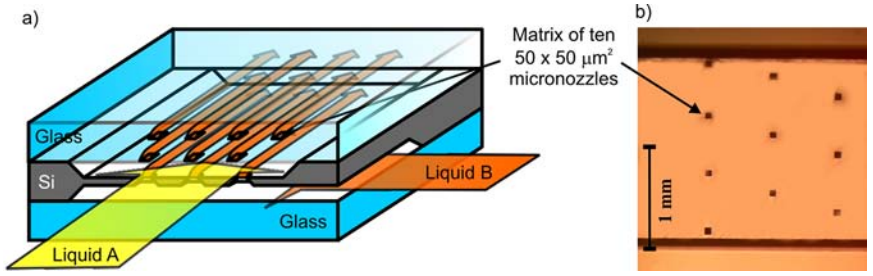

Figure 3. Multistream micromixer: (a) principle of work, (b) real view of the matrix of micronozzles.

Table 1. Screening experiments for the nitration of 2-isopropoxybenzaldehyde (4) using fuming HNO_3 in the microreactor

entry	R_t (s)	temp. (°C)	stoichiometric ratio (**4**:fuming HNO_3)	**4** (%)[a]	**5** (%)[a]	**7** (%)[a]	byproduct (%)[a,b]
1	129	25	1:9.25	0	64	20	16
2	129	25	1:6.47	0	69	24	7
3	129	0	1:6.47	17	62	21	0
4	151	0	1:6.47	15	60	25	0
5	151	−10	1:6.47	21	60	19	0
6	129	10	1:9.25	0	84	16	0
7	151	10	1:6.47	0	84	16	0
8	76	10	1:6.47	0	87	13	0
9	50	10	1:6.47	0	87	13	0
10	5.4	10	1:6.47	0	87	13	0

[a]Determined by GC analysis. GC retention time for **7** was 4.43 and for **5**, 6.50. [b]Baseline impurities in GC of which the structures were not confirmed.

defined, reaction times; hence, it has emerged as a useful tool for research and development chemists.[11] In the literature, there are quite a few examples describing efficient nitration reactions performed under continuous conditions.[12] Encouraged by these reports we decided to adapt our nitration reaction to continuous flow, and we demonstrated the high productivity of this process using a relatively simple setup. The core and most sophisticated element of the setup used here is a tailored, flow-through, silicon–glass microreactor, where a multistream micromixer, reaction channel, and large-area cooling chamber were integrated in a single chip (Figure 2). Moreover, the microreactor is equipped with five miniature temperature sensors on-chip integrated along the reaction channel. On-chip temperature measurements in tandem with the cooling chamber allow control of the reaction temperature with high precision.

The microreactor is a multilayered glass–silicon–glass structure fabricated by us with the use of microengineering techniques. Reaction channel, micromixer, and large-scale cooling chamber are anisotropically etched (10 M KOH at 80 °C) on both sides of a 3-in. silicon wafer. After this, the silicon body is covered on both sides by glass wafers utilizing a glass-to-silicon anodic bonding process as the assembling method. Special construction of the micromixer allows increasing the mixing efficiency (Figure 3). Liquid B is divided into 10 substreams and injected into the main stream of liquid

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A. In this way the contact surface between liquids A and B is multiplied, which consequently increases diffusion and mixing efficiency.

To our satisfaction, experiments with fuming nitric acid and with the use of the aforementioned microreactor gave excellent results in terms of yields and selectivity of the desired product (Table 1). We used 2-isopropoxybenzaldehyde (**4**) (2.5 M in CH_2Cl_2) as substrate in that process (Figure 4).[13]

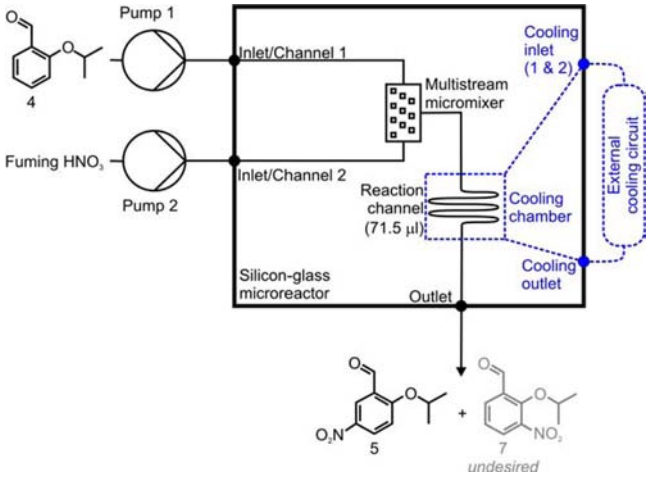

Figure 4. Setup for nitration reaction of 2-isopropoxybenzaldehyde (**4**) in continuous flow.

The screening quickly revealed that the temperature is crucial for the correct outcome of the process. The reaction proceeded to completion already at 10 °C. When the process was run at higher temperatures, undesired oxidation of 2-isopropoxy-5-nitrobenzaldehyde (**5**) to the corresponding carboxylic acid byproduct by HNO_3 used in excess was observed (Table 1, entries 1 and 2). In turn, lower temperatures led to incomplete conversion (Table1, entries 3−5). Finally, when reaction temperature was set at 10 °C and the stoichiometric ratio of **5**:fuming HNO_3 equal to 1:6.47 and residency time (R_t) of 76 s, we obtained an excellent 87% selectivity in the formation of the desired para isomer **5** (Table 1, entry 8) and those stoichiometric and temperature conditions were chosen for further optimization trials. The construction of the aforementioned microreactor does not allow any modifications in the length of the reaction channel; therefore, to further increase the productivity we continued to increase the flow rate until we reached the maximum R_t value of 5.4 s for which the selectivity and conversions were conserved (Table 1, entry 10). The longest run was performed using the latter conditions with an outlet flow of 47.6 mL/h. Extraction of the quenched reaction mixture gave crude product that, after washing with warm hexane, gave 65% yield (87% selectivity) of pure 2-isopropoxy-5-nitrobenzaldehyde (**5**). In total, 26 g of **5** was produced over 120 min (the longest run performed), giving a satisfactory production rate of 13 g/h. Importantly, not only were the screening experiments complete within a matter of days, but we also were able to produce a substantial amount of required pure material in just 1 h using the microreactor setup. The flow reaction shows a considerable time savings, high repeatability,[14] and better yield along with improved selectivity of the nitration process compared to those of the batch experiment.

CONCLUSIONS

We have demonstrated that nitration of 2-isopropoxybenzaldehyde (**4**) with red fuming HNO_3 in continuous flow can be performed with high selectivity and productivity, affording selectively the desired 2-isopropoxy-5-nitrobenzaldehyde (**5**), an important building block in the preparation of nitro-substituted Hoveyda−Grubbs metathesis catalyst. This example of challenging chemistry encountered by our research group, which showed problems on scale-up, transferred to continuous flow turned out to be more effective than the batch process in terms of reaction yield and selectivity, which in the case of continuous flow process reached an excellent 87%. In addition, optimization of the presented nitration process was possible in a rapid manner (within a 2-weeks time frame, including screening), using a relatively simple setup and with a productivity of 13 g/h. In summary, nitration in continuous flow provided us a safe alternative to running a dangerous exothermic reaction in batch and showed significant time savings, especially in the screening of reaction parameters to find the optimal conditions.

The here reported promising results of nitration of 2-isopropoxybenzaldehyde (**4**) with red fuming HNO_3 in continuous flow, motivated us to work on nitration processes for the chemical plant, utilizing flow-through microreactors. The Division of Microengineering and Photovoltaics is sufficiently powerful and experienced to design and fabricate the wafer-scale, silicon-glass microreactors and desktop chemical plants. In close cooperation with Apeiron Synthesis, new versions of microreactors are currently under development.

EXPERIMENTAL PROCEDURES

General. ^1H (300 MHz), ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance TM DRX (300 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane (Me_4Si, δ 0.0) for ^1H NMR, $CDCl_3$ (δ 77.0) for ^{13}C NMR. Coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer. HRMS analyses were performed on LCT Premier XE Waters apparatus, on mode ESI + (TOF MS ES+). All solvents for extractions and reactions were technical grade and were dried before use using standard techniques. All chemicals were used as received from the commercial supplier. Fuming nitric acid used was anhydrous, and concentration was 98%. GC was performed on Trace GC Ultra (Thermo Electron Corporation) equipped with HP-5 column. GC parameters: initial temperature 160 °C, initial time 1 min, ramp 10 °C/min, final temperature 220 °C, hold time 4.5 min.

Protocol for the Nitration of 2-Isopropoxybenzaldehyde (4) with Red Fuming HNO_3 - 100 g Scale. A three-necked, 1 L, round-bottom flask equipped with a stirring bar and dropping funnel was charged with fuming HNO_3 (121 mL, 2.844 mol) and cooled to −10 °C (ethanol−liquid nitrogen). A solution of 2-isopropoxybenzaldehyde (**4**) (100 g, 0.609 mol) in CH_2Cl_2 (200 mL) was added drop by drop over 2 h, maintaining the temperature of the reaction mixture at −10 °C. After the addition was complete, the reaction mixture was left to slowly warm to 10 °C over 10 h. After that time, the reaction mixture was poured into ice (250 g), and H_2O (150 mL) was added. The product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 5% aqueous NaOH (2 × 100 mL), H_2O (2 × 100 mL), and brine (2 × 100

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mL) and dried over anhyd. $MgSO_4$. Solvent was evaporated under vacuum, and the crude product (isomer ratio **5**:**7** equal to 75:25) was recrystallized from ethanol using the following procedure: The crude product was dissolved in hot ethanol (300 mL) and allowed to slowly cool down to room temperature (yellow crystals of the desired product **5** precipitated). The precipitate was filtrated, washed with hexane (3 × 25 mL), and dried on vacuum (83.43 g, 50%). Yellow, low-melting crystalline solid.[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 1.47 (d, 6H, J = 6.0 Hz), 4.83 (q, 1H, J = 6.0 Hz), 7.10 (d, 1H, J = 9.3 Hz), 8.40 (dd, 1H, J = 2.9, 9.2 Hz), 8.69 (d, 1H, J = 3.0 Hz), 10.41 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 21.9, 72.7, 113.4, 124.8, 125.0, 130.5, 141.0, 164.5, 188.0. IR (KBr): 3115, 2991, 2942, 1679, 1609, 1526, 1348, 1284, 1111, 950, 832, 748, 667 cm^{-1}. HRMS (EI) calcd for M + ($C_{10}H_{11}O_4N$): 209.0688. found 209.0689.

Protocol for the Nitration of 2-Isopropoxybenzaldehyde (4) with Red Fuming HNO_3 - 1 kg Scale. A 10 L Büchi minipilot reactor (series RWDE 20) equipped with PTFE anchor stirrer paddle was charged with fuming HNO_3 (1210 mL, 28.43 mol) and cooled to −10 °C (Huber Unistat 510 cooling/heating apparatus). A solution of 2-isopropoxybenzaldehyde (**4**) (1000 g, 6.08 mol) in CH_2Cl_2 (3000 mL) was added slowly over 4 h, maintaining the temperature of the reaction mixture at −10 °C (stirring 120 rpm). After the addition was complete, the reaction mixture was allowed to slowly warm to 10 °C over 10 h. After that time, ice (∼1000 g) and then H_2O (500 mL) were added to the reaction mixture. The product was extracted with CH_2Cl_2 (4 × 500 mL). The combined organic layers were washed with 5% aqueous NaOH (2 × 400 mL), H_2O (2 × 400 mL), and brine (2 × 500 mL) and dried over anhyd. $MgSO_4$. Solvent was evaporated under vacuum, and the crude product (isomer ratio **5**:**7** equal to 60:40) was recrystallized from ethanol using the following procedure: The crude product was dissolved in hot ethanol (2000 mL) and allowed to slowly cool down to room temperature (yellow crystals of the desired product **5** contaminated with unwanted isomer **7** precipitated). The precipitate was filtrated and washed with warm hexane (several times to remove the isomer **7** that is better soluble in hexane than is **5**). If necessary the recrystallization from hot ethanol can be repeated. The yield of the pure **5** was 30% (382 g) as a yellow, low-melting, amorphous solid.

Protocol for the Nitration of 2-Isopropoxybenzaldehyde (4) with Red Fuming HNO_3 in Continuous Flow Using Microreactor Described in This Work. The reagent stock bottles were filled with 2-isopropoxybenzaldehyde (**4**) in CH_2Cl_2 (2.5 M) and neat fuming nitric acid, respectively. The equipment (Ascor AP23 syringe pump) was set to flow with **4**/fuming HNO_3 ratio of 1:6.47. Syringe 1 delivered 28 mL/h of 2-isopropoxybenzaldehyde (**4**) solution and syringe 2 delivered 19.6 mL/h of fuming nitric acid to give a residency time of 5.4 s at 10 °C and a final outlet flow rate of 47.6 mL/h. The outlet stream was collected for 120 min and poured directly into ice water (1 L). When collection stopped, the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with aqueous 5% NaOH (3 × 50 mL) and brine (1 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration of drying agent and evaporation of solvent, the crude 2-isopropoxy-5-nitrobenzaldehyde (**5**) was isolated as a yellow solid. Washing with warm hexane afforded pure **5** (26 g) as pale-yellow crystals (65% yield). Rate of production = 13 g/h.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Description of the nitration process with the use of 2-hydroxybenzaldehyde (**2**) as substrate and detailed procedure for the fabrication of the microreactor used in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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