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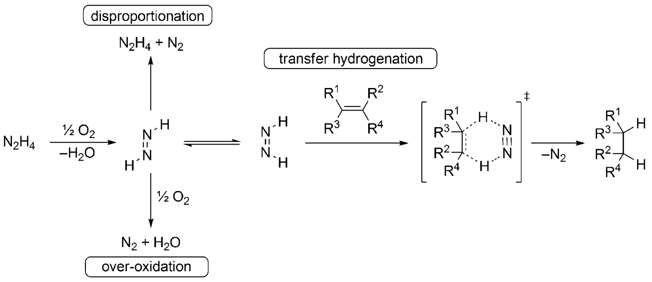
Flow Chemistry

In Situ Generation of Diimide from Hydrazine and Oxygen: Continuous-Flow Transfer Hydrogenation of Olefins**

*Bartholomäus Pieber, Sabrina Teixeira Martinez, David Cantillo, and C. Oliver Kappe**

In-situ-generated diimide (N_2H_2)[1] has been used as a transfer hydrogenation agent in synthetic organic chemistry for more than a century,[2] and its ability to selectively reduce unsaturated carbon–carbon bonds was already established in the early 1960s.[2] Investigations into its thermal stability demonstrated that diimide readily undergoes disproportionation to N_2 and hydrazine at temperatures around −180 °C.[2] The first direct evidence for the existence of diimide in the solution phase was obtained by Sellmann and Hennige who were able to trap the *trans* isomer as a diazene complex.[3] The most straightforward and atom-economical pathway for the generation of diimide is the oxidation of hydrazine using species such as H_2O_2, $NaIO_4$, $K_3[(FeCN)_6]$, or molecular oxygen as oxidants.[2] The generated diimide is then typically utilized in situ as a transfer hydrogenation agent for the highly selective reduction of unsaturated carbon–carbon bonds.[2] Compared to classical, transition-metal-catalyzed reduction processes involving hydrogen gas, this method often provides a useful alternative, owing to its extremely high selectivity.[4]

Synthetically useful methods for the oxidation of hydrazine with molecular oxygen generally require catalysts to enhance this transformation. Traditionally, copper salts were used to obtain high reaction rates,[2] whereas today, iron salts[5,6] and organocatalysts such as guanidine salts[7] or flavin derivatives are well-studied alternatives.[8] The generation of diimide by the oxidation of hydrazine with oxygen gas in the absence of a catalyst is also possible, even though significantly longer reaction times in combination with a high excess of hydrazine are often required, as the oxidation proceeds relatively slowly and the reactive intermediate is prone to disproportionation (reformation of hydrazine) and over-oxidation (Scheme 1).[2] In fact, Burgard and co-workers recently described the selective reduction of a terminal olefin (artemisinic acid), employing 3 equivalents of hydrazine hydrate in combination with synthetic air (5% v/v oxygen for safety reasons) on a pilot plant scale within 11 h at 40 °C.[9] A continuous process employing microreactors could potentially overcome these limitations by allowing intensified process conditions (such as high temperature/pressure) in a safe and controllable manner.[10] Importantly, biphasic gas–liquid continuous-flow processing in microreactors leads to extremely large and well-defined interfacial areas (in a segmented flow system) compared to the situation in conventional batch environments, and thus to a significantly enhanced mass transfer.[11]



Scheme 1. Aerobic oxidation of hydrazine to diimide and subsequent transfer hydrogenation, disproportionation, and over-oxidation.

Herein, we present a highly intensified and catalyst-free method for the in situ generation of diimide from hydrazine monohydrate ($N_2H_4{\cdot}H_2O$) and molecular oxygen in continuous-flow mode. The diimide generated by this novel gas–liquid flow system is applied to the selective reduction of a variety of alkenes to provide the corresponding alkanes in excellent yields and high selectivity.[12] Notably, the high surface-to-volume area in combination with high-temperature/high-pressure conditions (novel process windows)[13] results in remarkably short reaction times (10–30 min) employing only 4–5 equivalents of the hydrazine precursor.

The continuous-flow setup (Figure 1) consists of a pump (P), a mass-flow controller (MFC), a glass static mixer (GSM)

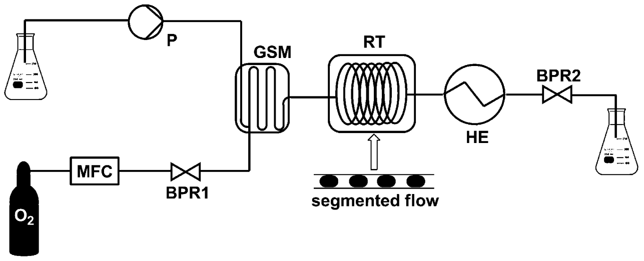


Figure 1. Continuous-flow setup for the in situ generation of diimide and subsequent olefin reductions. (for further details, see the Supporting Information).

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[*] B. Pieber, Dr. S. T. Martinez, Dr. D. Cantillo, Prof. C. O. Kappe
Christian Doppler Laboratory for Microwave Chemistry (CDLMC)
and
Institute of Chemistry, Karl-Franzens-University Graz
Heinrichstrasse 28, 8010 Graz (Austria)
E-mail: oliver.kappe@uni-graz.at
Homepage: http://www.maos.net

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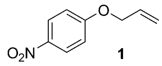
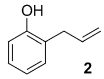
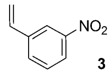
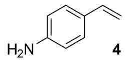
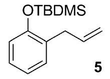
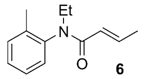
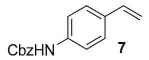
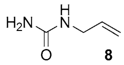
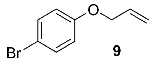
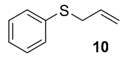
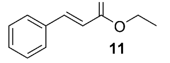
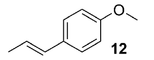
to generate segments of the liquid phase and O_2, a residence time unit (RT) made of perfluoroalkoxy copolymer (PFA), a heat exchanger (HE), and a static (BPR1) as well as an adjustable back pressure regulator (BPR2).[14] Preliminary experiments using ethanol as the solvent revealed that at a backpressure of 20 bar, a liquid flow rate of 0.4 mL min^{-1}, and a gaseous stream of 2 mL min^{-1} are necessary to maintain both a suitable segment pattern and a proper residence time (10 min).

The reduction of allylbenzene to propylbenzene was chosen as the model transformation for a detailed optimization study of the continuous process. Initially, a solvent screening was performed using a variety of alkyl alcohols and 5 equivalents of hydrazine monohydrate at different temperatures (Supporting Information, Table S1 and Figure S4). At 80 °C, a clear trend with respect to reaction rate (MeOH < EtOH < *i*PrOH < *n*PrOH < *n*-butanol < *n*-pentanol) was observed. The most reasonable explanation for this phenomenon is related to the increasing solubility of oxygen gas in this series of alcohols.[15] We therefore decided to utilize *n*PrOH for all further optimization experiments, as the conversions in this solvent were significantly higher than in MeOH, EtOH, or *i*PrOH, and the boiling point of *n*PrOH, compared to the higher homologues, is still low enough to allow for a convenient work up.

The allylbenzene model reaction was further tested at higher temperatures, resulting in a conversion of 94 % at 100 °C when using 5 equivalents of $N_2H_4{\cdot}H_2O$ (Table S2). To drive the reaction to completion and simultaneously increase the throughput, the substrate concentration was increased from 0.1 M to 0.5 M. This intensified process allowed us to reduce the amount of hydrazine hydrate to 4 equivalents while still maintaining quantitative conversion with perfect selectivity in only 10 min reaction time;[16,17] whereas lower amounts resulted in incomplete reactions, even at elevated temperatures. It has to be stressed that mixtures of oxygen and organic solvents have a rather high potential for explosions, and therefore the small volumes and channel dimensions of a continuous flow (micro)reactor minimizes possible flame propagation.[18] The installed heat exchanger cools the reaction mixture to ambient temperatures before depressurization. As anticipated, the use of synthetic air instead of O_2 resulted in dramatically reduced substrate consumption (53 %). Control experiments without hydrazine (< 1 % conversion) or nitrogen instead of oxygen (8 % conversion) were also carried out.

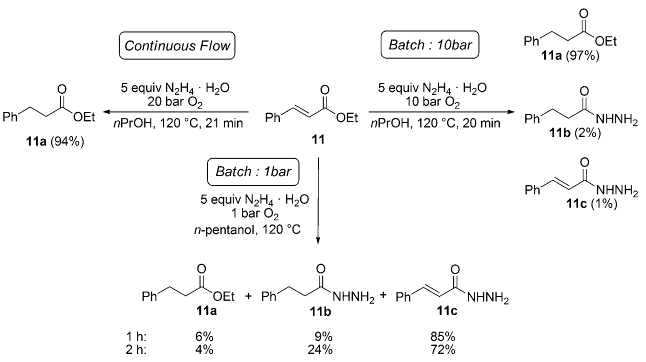
With the optimized conditions for allylbenzene in hand, we next evaluated the continuous-flow transfer-hydrogenation system for a variety of functionalized alkenes. The suitability of the substrates for the reaction was pre-evaluated through calculations at the M06-2X level[19] for the hydrogen transfer from *cis*-diimide to the corresponding olefin. Notably, the computational results provided valuable guidance prior to experimental assessment of the reactivity (Table 1; see also Table S4). Most of the chosen substrates (**1**–**5**, **7**, **9**) underwent total consumption without any need for reoptimization from the conditions used for allylbenzene, whereas some other olefins required a larger excess of hydrazine (**6**, **8**, **10**), or a combination of more hydrazine, longer reaction times, and slightly increased temperatures (**11**, **12**). In terms of selectivity, olefins containing nitro groups (**1**, **3**) resulted in the desired products in near quantitative yields.[20] Silyl ether protecting groups (**5**) and halogen atoms (**9**) easily resisted the applied conditions. Moreover, Cbz-protected amines (**7**; Cbz = benzyloxycarbonyl), which are prone to deprotection in transition-metal-catalyzed hydrogenations, were reduced in almost quantitative yields.[21] Carbonyl functional groups are somewhat critical when hydrazine is used as a reagent; somewhat surprisingly however, the reduction of ethyl cinnamate (**11**) afforded the desired product in almost quantitative yield without any detectable amount of the corresponding hydrazide.

Table 1: Reduction of olefins by diimide generated in situ from $N_2H_4{\cdot}H_2O$ and O_2 (Scheme 1).[a]

Entry	Substrate	$N_2H_4{\cdot}H_2O$ [equiv]	Conversion [%][b]	Selectivity [%][b]	Yield [%][c]
1		4	> 99	> 99	99
2		4	> 99	> 99	98
3		4	> 99	> 99	92
4		4	> 99	> 99	95
5		4	> 99	> 99	92
6		5	> 99	> 99	88
7[d]		4	> 99[e]	> 99[e]	87
8[f]		5	> 99[e]	> 99[e]	97
9		4	> 99	> 99	93
10		5	> 99	66[g]	58
11[h]		5	> 99	> 99	94
12[i]		5	> 99	> 99	91

[a] Conditions (unless otherwise noted): alkene (0.5 M, 0.5 or 1 mmol) in *n*PrOH, 0.4 mL min^{-1} liquid flow rate, 2 mL min^{-1} gas flow rate, 20 bar backpressure, at 100 °C, with a 10 min residence time (10 mL coil). [b] Given as percent of GC-FID peak area. [c] Yield of isolated product. [d] Conc. = 0.33 M. [e] Determined by ^{1}H NMR spectroscopy. [f] *n*PrOH/H_2O (1:1) as solvent. [g] Given as percent of HPLC peak area at 215 nm. [h] Run at 120 °C with a 20 min residence time (16 mL coil). [i] Run at 120 °C with a 30 min residence time (26 mL coil). Cbz = benzyloxycarbonyl, TBDMS = *tert*-butyldimethylsilyl.

A comparison study for the reduction of cinnamate **11** using a standard batch balloon method was carried out in *n*-pentanol to mimic the experimental conditions (120 °C) of the



Scheme 2. Comparison of continuous flow and both pressurized and atmospheric batch reductions of ethyl cinnamate **11** (conversions for batch experiments were determined by GC-MS peak-area integration).

continuous experiment (Scheme 2). Analysis of the reaction mixture revealed that in the batch experiment the majority of the cinnamate (**11**) reacted with N_2H_4, resulting in hydrazide **11c**, whereas only very small amounts of the saturated ester (**11a**) resulting from diimide reduction were obtained. With prolonged reaction time, hydrazide **11c** is reduced by diimide, resulting in 3-phenylpropanehydrazide (**11b**). This example highlights that the generation of diimide in the gas–liquid segmented flow reactor is dramatically enhanced and significantly faster than other processes, such as hydrazide formation. The same reaction was also carried out in a small-scale quartz autoclave using *n*-propanol at 120 °C and 10 bar O_2 pressure.[17] Under these conditions, a quantitative reaction was obtained within 20 min, resulting in the desired ester (**11a**) in good selectivity (97 %, Scheme 2; see also Figure S8). However, an autoclave experiment of this nature involving pure oxygen and a mixture of flammable organic solvent and hydrazine is of very limited practical use, owing to the high potential for explosions, which is minimized in the continuous approach.

To estimate the rate of oxidation of hydrazine and the stability of diimide under the gas–liquid reaction conditions, a set of additional experiments was designed. Using a modified continuous-flow setup with two separate residence time units and incorporating an additional liquid feed in between the two units (Figure 2; see also Figure S9), the consumption of hydrazine in the oxidation process was investigated. For this purpose, a 5.5 mL residence time unit was installed in which hydrazine monohydrate in *n*PrOH was allowed to react with oxygen at 100 °C in the absence of the olefin substrate. After the first residence time unit, a stream of benzaldehyde dissolved in *n*PrOH was introduced via a T-mixer and the mixture was passed through and collected after an additional residence time unit (6.5 mL, 100 °C). Notably, only very small amounts of the benzaldehyde trapping reagent were consumed, demonstrating that, under these intensified conditions, hydrazine was almost completely oxidized within the residence time of ca. 5 min in coil 1. Changing the first residence time unit to one with a smaller volume (2.5 mL, residence time ca. 2 min) resulted in a significantly higher conversion of benzaldehyde, thus indicating residual amounts of hydrazine in the reaction mixture.

When the same trapping experiments were repeated with 3-nitrostyrene (**3**) instead of benzaldehyde (in order to estimate the lifetime of diimide), 12 % of the reduced olefin were obtained utilizing the 2.5 mL coil. Only trace amounts of the transfer hydrogenation product were observed when the longer 5.5 mL coil was used, indicating that hydrazine was almost completely over-oxidized to nitrogen and water in the absence of an olefin substrate. This clearly demonstrates the extremely short lifetime of the diimide intermediate in solution phase, as well as the efficiency of the gas–liquid flow procedure.

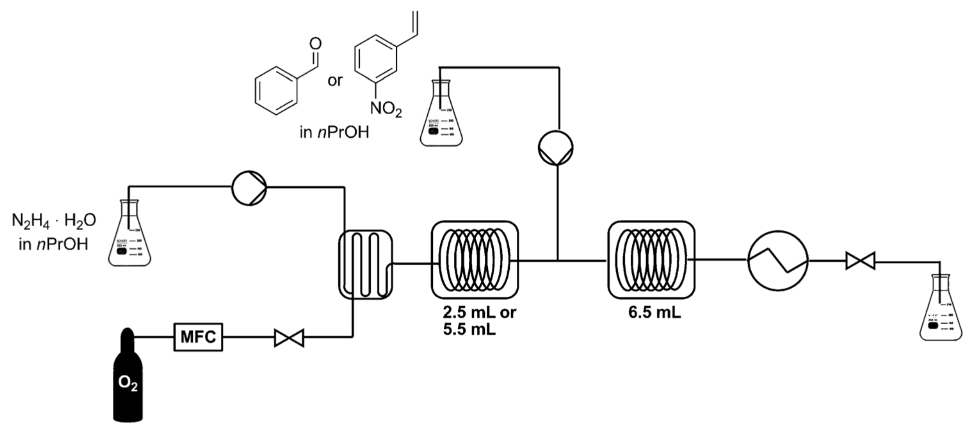


Figure 2. Continuous-flow setup for hydrazine trapping experiments with benzaldehyde or 3-nitrostyrene.

In summary, we have developed a highly efficient and catalyst-free process for the in situ generation of diimide from hydrazine hydrate and molecular oxygen and its application for the selective reduction of unsaturated carbon–carbon bonds. Key to the success was the use of a gas–liquid continuous-flow system, which enabled a catalyst-free reaction at high oxygen pressure in a safe and scalable way. The method described herein was shown to enable olefin reductions that cannot be reproduced using batch techniques at atmospheric pressure.

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Keywords: continuous flow · diimide · hydrazine · hydrogenation · oxygen

[1] Alternative names for diimide reported in the literature are diazene and diimine.

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[16] The only by-product observed in these experiments, according to GC-MS analysis, was a small amount of 1,2-dipropylidenehydrazine resulting from solvent oxidation and subsequent reaction with hydrazine (Figure S5).

[17] **Caution**: The reactions/reagents described herein have the potential to release large amounts of energy in an uncontrolled way. These oxidations should not be undertaken without stringent hazard assessment and proper safety precautions in place.

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[20] This remarkable selectivity is the result of performing the reaction in the absence of a metal catalyst. For an Fe-catalyzed, hydrazine-mediated method for nitro-group reduction, see: D. Cantillo, M. Baghbanzadeh, C. O. Kappe, *Angew. Chem.* **2012**, *124*, 10337; *Angew. Chem. Int. Ed.* **2012**, *51*, 10190.

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