EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Design and Development of Pd-catalyzed Aerobic N-Demethylation Strategies for the Synthesis of Noroxymorphone in Continuous Flow Mode

Authors: Bernhard Gutmann, David Cantillo, Ulrich Weigl, D Phillip Cox, and C. Oliver Kappe

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201601453

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601453

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

Full Paper

Design and Development of Pd-catalyzed Aerobic *N*-Demethylation Strategies for the Synthesis of Noroxymorphone in Continuous Flow Mode

Bernhard Gutmann,[a,b] David Cantillo,[a,b] Ulrich Weigl,[c] D. Phillip Cox[d] and C. Oliver Kappe*[a,b]

Abstract: Strategies for the generation of noroxymorphone from 14-hydroxymorphinone are presented. Noroxymorphone is the key intermediate in the synthesis of various opioid antagonists, including naloxone, naltrexone and nalmefene, as well as mixed agonists-antagonists like nalbuphine. The transformation requires removal of the *N*-methyl group from the naturally occurring opiates and a double bond hydrogenation. The pivotal reaction step thereby is a *N*-methyl oxidation with colloidal palladium(0) as catalyst and pure oxygen as terminal oxidant. The reaction produces a 1,3-oxazolidine intermediate, which can be readily hydrolyzed to the corresponding secondary amine. Different reaction sequences and various phenol protection groups were explored. The most direct route consumes only H_2, O_2 and H_2O as stoichiometric reagents and produces only H_2O as by-product. Challenges inherent in gas-liquid reactions with oxygen as oxidant were addressed by developing a continuous flow process.

[a,b] *Dr. B. Gutmann, Prof. Dr. C. O. Kappe*
Institute of Chemistry, University of Graz, NAWI Graz
Heinrichstrasse 28, 8010 Graz (Austria)
and Research Center Pharmaceutical Engineering (RCPE)
Inffeldgasse 13, 8010 Graz (Austria)
E-mail: oliver.kappe@uni-graz.at
Homepage: http://goflow.at

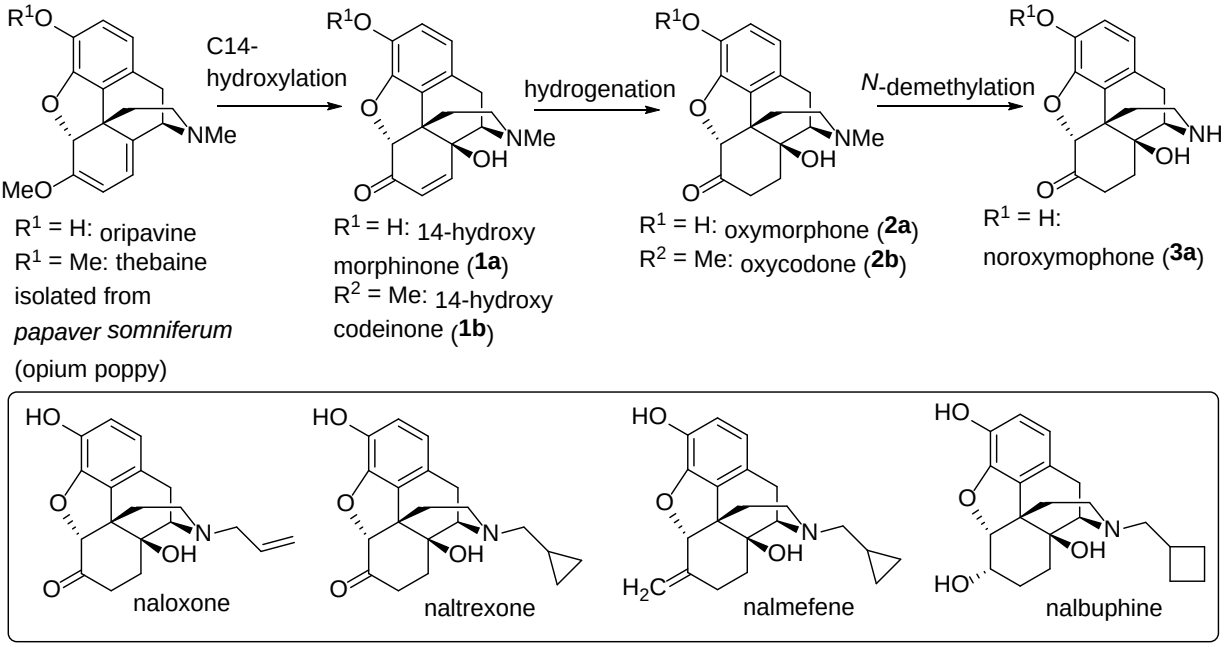
[c] *Dr. U. Weigl,*
Cilag AG
Hochstrasse 201, 8200 Schaffhausen (Switzerland)

[d] *Dr. D. P. Cox*
Noramco Inc.
503 Carr Rd, Suite 200, Wilmington DE 19809 (USA)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201601453.

Introduction

In the past 15 years, the number of deaths associated with medical and nonmedical use of opioids increased dramatically.[1,2] In response to the epidemic, intensified and coordinated drug prevention efforts have been initiated. In particular, these efforts have included measures to expand and ease access to opioid antagonists.[1] Naloxone is the most important opioid antagonist and it is on the World Health Organization's List of Essential Medicines. Within a few minutes, it fully reverses the effects of many natural as well as synthetic and semi-synthetic opioids by effectively displacing them at the μ-opioid receptor. Naloxone is an uncontrolled substance with no potential for abuse or overdose. It is usually administered by intravenous or intramuscular injection. In addition, intranasal formulations have become available recently.[2] A longer-acting opioid antagonist is naltrexone. Naltrexone and its derivative, nalmefene, are primarily used in the management of opioid and alcohol dependence. Both naloxone and naltrexone are formally derived from oxymorphone (**2a**) by *N*-demethylation and re-alkylation (Scheme 1). The direct product of the *N*-demethylation of oxymorphone (*i.e.* noroxymorphone **3a**, Scheme 1) is indeed the key intermediate in the synthesis of various opioid antagonists, including naloxone, naltrexone and nalmefene, as well as mixed agonists-antagonists like nalbuphine (Scheme 1).[3-5] Oxymorphone, in-turn, can be prepared by well-developed procedures from naturally occurring opioids (*i.e.* oripavine and thebaine, Scheme 1). The most challenging transformation in this reaction sequence is the selective removal of the tertiary *N*-methyl group from the complex and highly functionalized morphine structure. Standard procedures for *N*-demethylation rely on strong electrophiles to first convert the tertiary amine into a quaternary ammonium ion.[3,4] A subsequent nucleophilic replacement of the methyl group from the ammonium ion affords the demethylated product. Typical electrophiles are cyanogen bromide (von Braun reaction),[3] and chloroformates,[4] forming respectively cyanamides and carbamates as intermediates, which are finally hydrolyzed to the corresponding secondary amines. Alternatively, oxidation of the alkaloid to the corresponding *N*-oxide (typically by peracids) and subsequent dehydration affords the demethylated product (Polonovski-type reaction).[5] These methods generally produce the desired secondary amines in moderate to high yields. However, since highly toxic and corrosive reagents in stoichiometric amounts are required and, consequently, stoichiometric amounts of waste products are generated, these processes have become increasingly unacceptable.



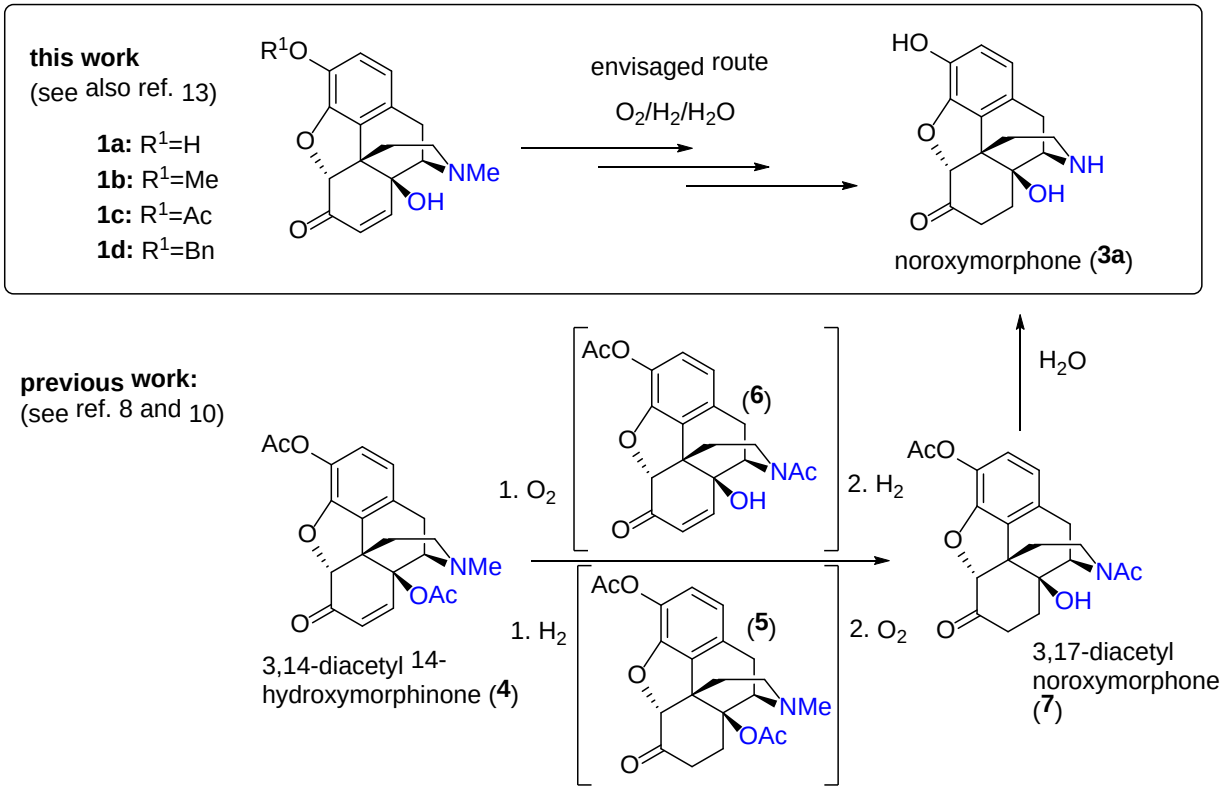
Scheme 1. Preparation of semisynthetic opiates from naturally occurring oripavine (or thebaine) with 14-hydroxymorphinone (**1a**) and noroxymorphone (**3a**) as intermediates.

In 2008, Hudlicky and coworkers demonstrated that the *N*-methyl group of hydrocodone can be removed by a palladium-catalyzed oxidation using oxygen as the terminal oxidant.[6] With 10 mol% $Pd(OAc)_2$ as catalyst and dioxane/acetic anhydride as solvent, *N*-acetyl norhydrocodone was obtained after 15 h at 80 °C. In subsequent publications, the Hudlicky group has shown that the reaction can be extended to certain other morphine alkaloids such as 3,14-diacetyl oxymorphone using oxygen under atmospheric pressure (**5**, Scheme 2).[7,8] The demethylation of diacetyl oxymorphone is accompanied by intramolecular 14-*O*- to 17-*N*-acetyl migration to form the 3,17-diacetylnoroxy derivative as the immediate product (**7**, Scheme 2).[8] A subsequent hydrolysis with 6M HCl finally yielded the desired noroxymorphone **3a**. (Scheme 2).[8]

From an environmental and economic perspective, molecular oxygen is the ideal oxidant.[9] However, gas-liquid reactions with pure oxygen on preparative scales are nearly absent in the pharmaceutical industry. In a review on large-scale oxidations in the pharmaceutical industry, process research chemists at Pfizer pointed out that "*perhaps the greatest factor influencing the hesitation to employ oxidation reactions on a large scale is the safety of these processes*".[9] Our group has recently presented a continuous flow protocol for the palladium-catalyzed *N*-demethylation of 3,14-diacetyl oxymorphone (**5**) and 3,14-diacetyl 14-hydroxymorphinone (**4**, Scheme 2).[10] By performing the oxidation in a continuous flow reactor,

process challenges inherent to gas-liquid reactions with pure oxygen are greatly alleviated.[11,12] Most importantly, combustion and explosion hazards are significantly reduced in continuous flow reactors.[11,12] Indeed, the protocol developed on a laboratory scale was readily scaled up to a 100 mL flow reactor, consisting of two gas-liquid micromixers -to ensure efficient gas-liquid mixing- and two tubular reactor modules, to provide residence volume.[10] Oxidation of 3,14-diacetyl 14-hydroxymorphinone (**4**) in the flow reactor, subsequent hydrogenation in a continuous flow packed bed reactor, and final hydrolysis in a batch reactor afforded the desired noroxymorphone **3a** in high quality and good overall yield on a kg-scale (Scheme 2).[10]

Interestingly, the oxidative *N*-demethylation with palladium acetate as catalyst generally fails for 14-OH unprotected 14-hydroxy opioids. However, we have recently demonstrated that, while no reaction occurs in the presence of $Pd(OAc)_2$, the oxidation of the *N*-methyl group of unprotected 14-hydroxymorphinone (**1a**) does proceed using palladium(0) colloids in polar aprotic solvents.[13] The direct demethylation of 14-OH unprotected 14-hydroxy opioids has considerable advantages. In particular, the final amide hydrolysis can be omitted when unprotected 14-hydroxy opioids are used as starting materials (Scheme 2). The hydrolysis of the amide requires heating of the opioid (**7**) to high temperatures under highly acidic conditions, and significantly reduces the yield of the synthesis route.[10] Herein we provide a full account of our research on the palladium-catalyzed oxidative *N*-demethylation of 14-OH unprotected hydroxy opioids.[13] Different reaction sequences and various phenol protection groups were evaluated to advance progress towards a selective and scalable synthesis of noroxymorphone **3a** starting from 14-hydroxymorphinone **1a**.



Scheme 2. Synthetic strategies for the generation of noroxymorphone (**3a**). Oxidation/hydrogenation or hydrogenation/oxidation of diacetyl protected hydroxymorphinone **4** proceeds via **6** or **5** as intermediates.

Results and Discussion

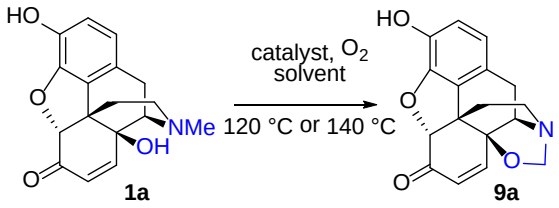
1. *N*-Demethylation/hydrogenation sequence

1.1. Batch optimization reactions. As shown in our preliminary report, no *N*-demethylation reaction occurs with 14-hydroxymorphinone **1a** as substrate and $Pd(OAc)_2$ as catalyst.[13] In contrast, an extensive screening of reaction conditions revealed that *N*-methyl oxidation does proceed in polar aprotic solvents, such as *N*,*N*-dimethylacetamide (DMA) and dimethyl sulfoxide (DMSO), in the presence of various palladium(0) species, including palladium(0) on charcoal or commercial unsupported palladium(0) particles (Table 1, entries 1 to 4). Thorough analysis of the crude reaction mixture revealed that the product of the palladium catalyzed oxidation is not the expected hydroxynormorphinone (**8a**, *c.f.* Scheme 4). Instead, the product formed in this reaction was the 1,3-oxazolidine **9a** (Table 1). The formation of related oxazolidines upon treatment of oxycodone- and oxymorphone-*N*-oxide with Burgess reagent as dehydrating agent was previously reported by Hudlicky and co-workers.[14] Notably, the reaction reported herein

accomplishes the formation of 1,3-oxazolidines in a one-step procedure with oxygen as the only stoichiometric oxidant and water as the only by-product.

A faster but somewhat less selective reaction was observed with platinum(0) species, such as platinum on charcoal (Table 1, entries 6 and 7). Solvents other than DMA and DMSO, including dioxane, ethyl acetate, acetonitrile, toluene and butanone, afforded no conversion or low conversions with poor selectivities.[13] Analogous results were obtained with 14-hydroxycodeinone **1b** (Table S1 in the Supporting Information).

Table 1. Screening of batch oxidation of 14-hydroxymorphinone **1a** with Pd(0) or Pt(0) under an O_2 atmosphere.[a]



	solvent	cat [mol%]	temp [°C]	time [min]	conv [%][b]	sel [%][b]
1	DMA	Pd/C(10)	140	40	73	96
2	DMSO	Pd/C(10)	140	40	>99	75
3	DMSO	Pd/C(10)	120	40	93	92
4	DMA	Pd black (10)	140	45	75	95
5	DMF	Pd black (10)	140	45	66	95
6	DMA	Pt/C(5)	140	45	>99	86
7	DMA	Pt/C(2.5)	140	45	84	93

[a] Conditions: 0.2 mmol of substrate **1a** and catalyst in 0.6 mL solvent were stirred under an O_2 atmosphere (balloon) on a hot-plate at 120 or 140 °C. [b] Conversion and selectivity were determined by HPLC-UV/VIS analysis (215 nm) after derivatization with benzyl bromide (see Scheme S1 in the Supporting Information and Experimental Section for details).

Colloidal Pd(0) particles are readily generated in solution by heating a Pd(II) source (*e.g.* $Pd(OAc)_2$) at temperatures above about 100 °C.[15] Indeed, experiments performed in our laboratory revealed that black solutions of palladium(0) particles can be formed by heating $Pd(OAc)_2$ for 2 to 10 min at temperatures of 120 to 140 °C in DMA as solvent.[13] The addition of acetic acid further stabilizes the colloidal palladium(0) and prevents its agglomeration and precipitation on the vessel walls.[13] Importantly, with 14-hydroxymorphinone **1a** dissolved in the

dark solutions of colloidal palladium(0), a fast and selective oxidation to the oxazolidine **9a** occurred. It should be emphasized that $Pd(OAc)_2$ is not reduced to Pd(0) under the applied reaction conditions in the presence of unprotected 14-hydroxy opioids (**1a**,**1b**). Accordingly, no oxidation reaction ensues. This is in contrast to reactions with 14-*OH*-protected 14-hydroxy opioids, such as 3,14-diacetyl hydroxymorphinone or 3,14-diacetyl oxymorphone (**4** and **5**).[10] Solutions of $Pd(OAc)_2$ and *OH*-protected 14-hydroxy opioids quickly become black upon heating in DMA as solvent, indicating the formation of palladium(0) colloids, and a clean demethylation reaction takes place.[8,10] Apparently, unprotected 14-hydroxy opioids stabilize palladium(II) and prevent the formation of catalytically active Pd(0).

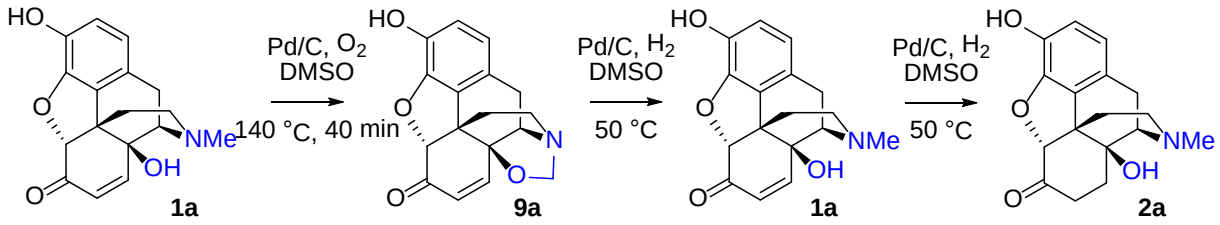
For oxidation reactions, $Pd(OAc)_2$ and AcOH were heated in DMA for 10 min at 120 °C to generate deep black solutions of finely dispersed colloidal Pd(0). 14-Hydroxymorphinone **1a** was then dissolved in this mixture and the mixture was again heated under an atmosphere of oxygen (O_2 balloon). A thorough optimization of the reaction conditions revealed that the reaction proceeds with high selectivity to conversions >95% after reaction times of only 30 min at 120 °C when 3 equiv of AcOH (with respect to the substrate) and 2.5 mol% of catalyst are used.[13] Reactions with air under atmospheric pressure instead of oxygen gave slightly reduced reaction rates (~80 min for complete conversion at 120 °C), whereas in the absence of oxygen, the reaction did not proceed (Table 2, entry 3 and 4). During the course of the reaction, the oxazolidine **9a** precipitated from the reaction mixture and was isolated in analytically pure form in ca. 80% yield by filtration. Increasing the scale of the reaction decreased the reaction rate appreciably. Nevertheless, for a reaction on a 500 mg scale with 5 mol% $Pd(OAc)_2$ as pre-catalyst, a conversion >95% was obtained after a reaction time of 2 h at 120 °C. The mixture was subsequently cooled to room temperature and the precipitate was isolated by simple filtration in 82% yield. The corresponding reaction with 14-hydroxycodeinone **1b** on a 100 mg scale yielded the oxazolidine **9b** with comparable purity after extraction with $CHCl_3/H_2O$ (95% yield). Similar results as with DMA/AcOH/$Pd(OAc)_2$ were obtained with Pd/C in DMSO as solvent. A batch reaction with hydroxymorphinone **1a** on a 1 g scale in DMSO as solvent with 5 mol% Pd/C as catalyst and O_2 as oxidant (balloon) required 40 min at 140 °C for complete conversion. After the reaction, the palladium catalyst was recovered by hot filtration. Water was then added to the filtrate to precipitate the oxazolidine **9a** in 77% yield. Interestingly, even though Pd(0) particles are formed upon heating of $Pd(OAc)_2$ in DMSO as solvent, the resulting mixture did not exhibit any catalytic activity for the *N*-methyl oxidation of 14-hydroxymophinone (Table 2, entry 5).

Table 2. Batch oxidation of 14-hydroxymorphinone (**1a**) with $Pd(OAc)_2$ as pre-catalyst at 120 °C in DMA or DMSO as solvent (30 min reaction time).[a]

	solvent	$Pd(OAc)_2$ [mol%]	oxidant	conv [%][b]
1	DMA	2.5	O_2	96
2	DMA	2.5	air	60
3	DMA	5.0	argon	4
4	DMA	100.0	argon	3
5	DMSO	5.0	O_2	0

[a] Conditions: 60 mg substrate, 3 equiv of AcOH, $Pd(OAc)_2$ in 0.6 mL solvent. $Pd(OAc)_2$ and the acetic acid in the solvent were heated in the absence of the substrate prior to the oxidation to generate colloidal palladium(0) particles (10 min at 120 °C). [b] Conversion was determined by LC-MS analysis and peak area integration of the extracted-ion chromatograms (see Experimental Section for details).

The next reaction steps for the generation of noroxymorphone **3a** are hydrogenation and hydrolysis of the oxazolidine **9a**. To explore whether the palladium(0) catalyst used for the oxidation of the methyl group could directly serve as catalyst for the subsequent hydrogenation, a batch reaction of 14-hydroxymorphinone **1a** with 5 mol% Pd/C in DMSO as solvent under an O_2 atmosphere (balloon) was performed. Complete conversion to the oxazolidine **9a** was obtained after a reaction time of 40 min at 140 °C on a 200 mg scale. The reaction mixture was then cooled to 50 °C and the O_2-balloon was replaced by a H_2-balloon. The Pd/C catalyst was indeed active for the hydrogenation. However, the main product formed after a reaction time of 90 min was identified as the 14-hydroxymorphinone **1a** (see Scheme 3 and Table S2 in the Supporting Information). Longer reaction times converted most of the 14-hydroxymorphinone **1a** to oxymorphone **2a**. The anticipated di-hydro oxazolidine product **10a** (*c.f.* Scheme 7) was not detected in the crude reaction mixture, indicating that hydrogenolysis of the oxazolidine ring is faster than hydrogenation of the C7-C8 double bond of the oxazolidine **9a** under these reaction conditions.



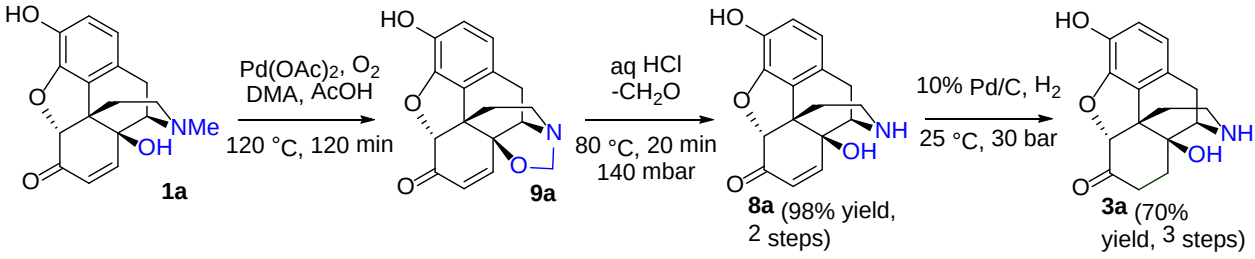
Scheme 3. Batch aerobic oxidation and subsequent hydrogenation of 14-hydroxymorphinone (**1a**) with Pd/C in DMSO.

To avoid hydrogenolysis of the oxazolidine ring, a reaction sequence consisting of oxidation, hydrolysis and subsequent hydrogenation was evaluated. Hydrolysis of the oxazolidine **9a** to 14-hydroxynormorphinone (**8a**) was expected to proceed quickly and cleanly. Indeed, LC-MS analysis suggested that the oxazolidine hydrolyses to the free amine on the HPLC column using MeCN/H_2O with 1 vol% of trifluoroacetic acid as eluent (the retention time and recorded mass of samples of oxazolidines **9** were those of the corresponding nor-derivatives **8**). Surprisingly, however, hydrolysis of the isolated oxazolidine **9a** in aqueous HCl proceeded only slowly and produced several side-products. One of the side-products arose from acid-catalyzed, conjugate addition of water to the enone (8-hydroxy-noroxymorphone **11**; *c.f.* Scheme 5). Further side-products were probably derived from a reaction of the electron rich A ring of the opioid with formaldehyde (*c.f.* Marquis reagent).[16] We hypothesized that the oxazolidine is in equilibrium with the free amine and formaldehyde. On the HPLC column the free amine and the formaldehyde are continuously separated by chromatography, driving the hydrolysis to rapid completion and preventing undesired side reactions. This hypothesis was further supported by the observation that the oxazolidine is acetylated quickly and selectively to the 3,17-diacetyl hydroxynormorphinone (**6**, Scheme S1 in the Supporting Information). Importantly, the reaction was considerably faster under reduced pressure. While the conversion was 53% after 80 min at 80 °C at atmospheric pressure, 77% conversion was obtained after a reaction time of only 4 min at 80 °C and a pressure of 140 mbar.[13] The reaction selectivity was around 90% for these reactions.

The palladium-catalyzed oxidation and hydrolysis can be readily combined in a two-step one pot procedure (Scheme 4). After the palladium catalyzed oxidation of 14-hydroxymorphinone **1a**, the reaction mixture was diluted with the same volume of 1N aqueous HCl to provide a dark homogeneous solution. The reaction mixture was subsequently heated under reduced pressure to hydrolyze the oxazolidine **9a** to the 14-hydroxynormorphinone **8a** (140

mbar within 20 min at 80 °C). This step was most conveniently performed in a rotary evaporator. From a reaction on a 500 mg scale, the desired 14-hydroxynormorphinone product **8a** was isolated by precipitation with 25% ammonia in 98% yield (93.5% purity according to HPLC-UV/Vis at 205 nm).

Finally, the full reaction sequence from 14-hydroxymorphinone **1a** to noroxymorphone **3a** was explored (Scheme 4). Since the palladium from the oxidation step partly precipitates from the mixture upon hydrolysis of the oxazolidine **9a**, an additional catalyst source was required for hydrogenation. Thus, the crude reaction mixture after oxidation and hydrolysis was pumped through a fixed-bed flow hydrogenator using palladium catalyst cartridges (Thales H-Cube Pro™).[17] Preliminary experiments showed that complete hydrogenation of the 14-hydroxynormorphinone **8a** to the noroxymorphone **3a** was obtained with a flow rate of 0.4 mL/min with a 10% Pd/C catalyst cartridge at a reaction temperature of 25 °C and a H_2 pressure of 30 bar. The collected sample was diluted with distilled water and crude noroxymorphone **3a** was precipitated with aqueous NH_3 to produce the desired product in 70% yield (92.8% purity by HPLC-UV/Vis at 205 nm).



Scheme 4. *N*-Demethylation of 14-hydroxymorphinone **1a** and subsequent hydrolysis and hydrogenation to noroxymorphone **3a**.

1.2. Continuous flow oxidation in a packed bed reactor. As a first approach we explored a continuous flow oxidation in a packed bed reactor. The experimental reactor consisted of an HPLC pump for introducing the liquid feed (Figure 1). Oxygen gas from a gas cylinder was fed into the system via a mass flow controller. The gaseous and liquid feed were combined in a stainless steel T-connector, and the combined mixture then passed through a stainless steel catalyst cartridge (ThalesNano CatCart®). The cartridge was packed with either 5% platinum-on-charcoal, or 5% palladium on an alumina support. The processed mixture finally left the system through an adjustable back-pressure regulator. Even though the catalyst bed, and thus the residence time, was very short (residence times in the order of seconds), high single pass

conversions were obtained with 14-hydroxycodeinone **1b** as starting material at reaction temperatures of 120 to 140 °C. For instance, with Pt/C at a reaction temperature of 120 °C, a conversion well above 90% was obtained with flow rates of 0.3 and 5 mL/min (gas flow at normal conditions) for the liquid and O_2 phase, respectively (Table S3 in the Supporting Information). However, the effluent mixture was colored deep black, indicating leaching of catalyst from the bed, and the performance of the catalyst quickly deteriorated for successive reactions. Furthermore, even though HPLC analysis suggested good selectivity, the product content in the crude reaction mixture after evaporation of the solvent was only ~45% (determined by ^{1}H-NMR with internal standard). Presumably, some of the product was adsorbed on the catalyst bed. Reactions with Pd/Al_2O_3 provided slightly lower conversions. Again, catalyst performance decreased rapidly (Table S3 in the Supporting Information).

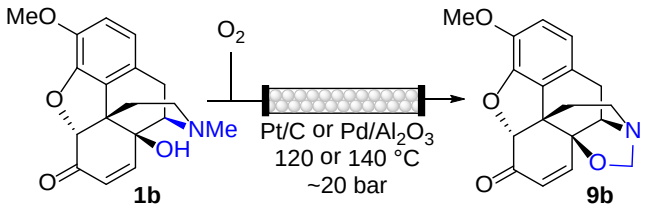


Figure 1. Packed bed reactor set-up.

1.3. Continuous flow oxidation in a gas-liquid tubular reactor. For further reactions, the catalyst cartridge was replaced by a residence tube reactor (Figure 2). For these reactions, $Pd(OAc)_2$ was heated in the presence of AcOH for 10 min to 120 °C to generate palladium(0) colloids. 14-Hydroxymorphinone **1a** was then dissolved and the mixture was loaded into the injection loop of the flow system. As residence reactor we employed a thick-walled, gastight fluoropolymer tube with 1.6 mm inner diameter (RT in Figure 2; fluorinated ethylene propylene (FEP), 1/8'' o.d., 1.6 mm i.d.). In order to transport the reaction mixture through the back pressure regulator as a homogeneous solution, 1N HCl was fed into the reactor before the back pressure regulator.[18] Any oxazolidine precipitate moved through the FEP reactor and dissolved upon mixing with aqueous HCl before the pressure regulator. No buildup of pressure or pressure oscillations were observed for flow reactions on the intended scales (up to ~1 g). The reaction mixture finally exited the system through a short cooling loop (stainless steel, 1/16'' o.d., 1 mm i.d.) and an adjustable back-pressure regulator.

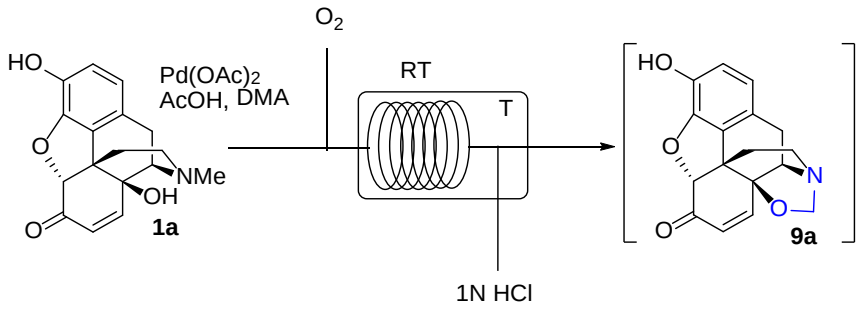


Figure 2. Schematic diagram of the flow reactor for aerobic oxidation.

Initial experiments were performed with a reactor of 10 mL residence volume and flow rates of 5 and 0.5 mL/min for the O_2 and liquid feed, respectively (stoichiometric ratio of O_2 to **1a** = 1.3). Conversions of around 90% with selectivities for the oxazolidine well above 90% were obtained after residence times of only ~10 min at 120 °C employing 1.25 mol% $Pd(OAc)_2$ as pre-catalyst (Table 3, entry 1; Table S4 in the Supporting Information). Additional flow reactions were performed in a reactor of 57 mL residence volume. Consistent conversions of ~90% to 96% were obtained with back pressures of around 6 to 10 bar and residence times of 10 to 25 min (Table 3). Increasing the amount of $Pd(OAc)_2$ from 1.25 to 2 mol% did not increase the conversion significantly, but the purity of the reaction decreased appreciably (Table 3, entries 2 to 4). Furthermore, increasing the residence time by decreasing the flow rate did not drive the reaction to higher conversions, while increasing the reaction temperature to 130 °C decreased the conversion (Table S4 in the Supporting Information). Finally, varying the pressure (Table 3, entries 5 to 8), or the amount of O_2 did not have any noticeable effect (Table S4 in the Supporting Information). Possibly, palladium is slowly oxidized to an inactive Pd(II) species and, as a consequence, the reaction comes to an end. As described above, Pd(II) is generally not active for the oxidation reaction and does not form catalytically active Pd(0) in the presence of 14-hydroxy opioids. Large amounts of oxazolidine **9a** precipitate formed for reactions performed at reaction temperatures below 120 °C and ultimately clogged the flow reactor.

After the reaction, the processed reaction mixtures were heated for 20 min in a rotary evaporator at 80 °C at a pressure of 140 mbar. Precipitation with ammonia after diluting with water and subsequent filtration provided the crude 14-hydroxynormorphinone (**8a**) as a solid in yields of around 70% (Table S4 in the Supporting Information). Direct hydrogenation in the Thales H-Cube Pro™ (see above) after a flow oxidation and hydrolysis on a 600 mg scale,

provided 403 mg of the crude product after precipitation with aqueous NH_3 (70% yield). The purities of the isolated products were comparable to those obtained for batch reactions.

Table 3. Flow oxidation of 14-hydroxymorphinone (**1a**) with $Pd(OAc)_2$ at 120 °C in DMA as solvent (stoichiometric ratio of O_2 to **1a** = 1.3).[a]

	res volume [mL]	$Pd(OAc)_2$ [mol%]	flow rate O_2/liquid[b] [mL/min]	p [bar]	res time [min]	conv [%][c]	sel [%][c]
1	10	1.25	5/0.5	9	11	89	93
2	57	1.25	20/2	10	13	91	93
3[d]	57	1.5	20/2	10	15	92	89
4	57	2	20/2	10	13	95	85
5	57	1.25	10/1	8	27	96	90
6[e]	57	1.25	10/1	7	24	96	94
7	57	1.25	10/1	6.5	21	96	94
8	57	1.25	10/1	6	19	94	94

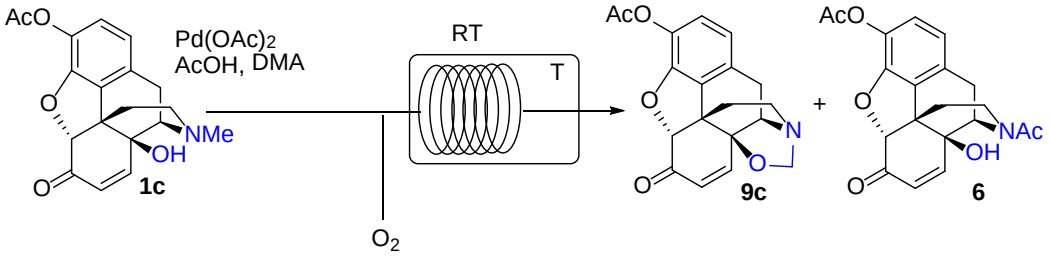
[a] Conditions: substrate (600 mg), AcOH (3 equiv), DMA (6 mL) and $Pd(OAc)_2$; the reaction mixtures were heated in the absence of the substrate for 10 min at a temperature of 140 °C before the continuous flow reaction to generate colloidal Pd(0) particles. [b] Flow rate gaseous and liquid phase (gas flow at normal conditions, *i.e.* T_n = 0 °C and p_n = 1 atm); 1.3 equiv of oxygen. [c] Conversion and selectivity was determined by HPLC-UV/Vis peak area integration at 215 nm after derivatization with Ac_2O (see Experimental Section for details). [d] Substrate (1200 mg). [e] Experiment was performed in triplicate providing identical results.

1.4. Phenol protection. One of the main impurities generated during the continuous flow oxidation was identified as a dimer derived from oxidative phenol coupling (Table S4 in the Supporting Information). In order to reduce oxidative dimerization, reactions with 3-OH protected 14-hydroxymorphinones were explored. 3-Acetyl-14-hydroxymorphinone **1c** can be prepared in high selectivity and close to quantitative yield from14-hydroxymorphinone **1a** by acetylation with 1 equiv of Ac_2O in the presence of 1 equiv of K_2CO_3 in THF as solvent (97% product yield).[14a] Importantly, both **1c** and the corresponding oxazolidine **9c** are soluble in DMA at the envisaged concentrations.

Continuous flow oxidations were performed in the same setup as shown in Figure 2, but without the HCl quench feed. The palladium-catalyzed oxidations with the 3-acetyl protected 14-hydroxymorphinone **1c** proceeded essentially as fast as reactions with unprotected **1a**. Conversions >90% were obtained after residence times of ~20 min with 1.25 mol% palladium acetate as pre-catalyst. The reaction was very clean with the main side-product being the 3,17-diacetyl-14-hydroxynormorphinone (**6**). This side-product probably arises from a transfer of the

acetyl group from the phenolic OH to the amine. Similarly as for reactions with unprotected 14-hydroxymorphinone **1a**, increasing the residence time or increasing the catalyst loading did not improve conversion (Table 4). Furthermore, varying the pressure or the equivalents of O_2 did not have an appreciable effect on reaction conversion or reaction selectivity (for further results see Table S5 in the Supporting Information). Significantly lower conversions were obtained when substrate, $Pd(OAc)_2$, and acetic acid in DMA as solvent were directly injected into the flow reactor, indicating the importance of prior formation of palladium(0) particles (Table S5 in the Supporting Information). The reaction was finally repeated under the best conditions (2.5 mol% $Pd(OAc)_2$, 6 equivalents of AcOH) on a 6 gram scale. The product was formed with good selectivity and high conversion (98%). Again, the main side-product in this reaction was the 3,17-diacetyl-14-hydroxynormorphinone **6** (4.2%). Figure S1 in the Supporting Information displays the HPLC-UV/Vis chromatogram of the crude reaction mixture.

Table 4. Flow oxidation of 3-Acetyl-14-hydroxymorphinone **1c** with oxygen.[a]

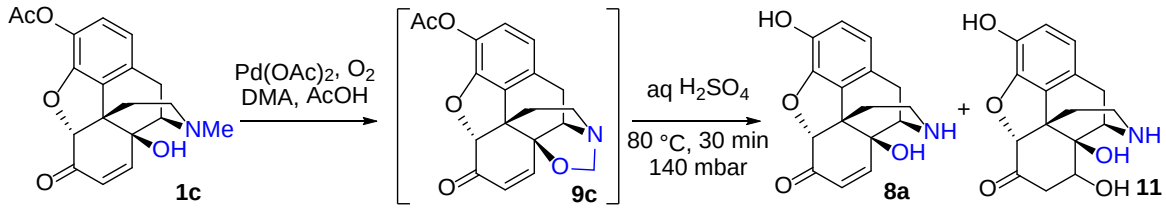


	$Pd(OAc)_2$ [mol%]	flow rate O_2/liquid [mL/min]	temp [°C]	p [bar]	res time [min]	conv [%][b]	sel [%][c]	**6** [%][c]
1	1.25	10/1	120	7	22	93	97	1.2
2	1.25	5/0.5	120	7	52	92	95	1.5
3	2.0	10/1	120	7	23	91	96	2.0
4	2.0	10/1	110	7	23	88	97	1.2

[a] Conditions: Ac-14-HM (600 mg), AcOH (3 equiv), DMA (6 mL) and $Pd(OAc)_2$; activation 20 min at 140 °C; pressure: 7 bar. [b] Conversion was determined by HPLC-UV/Vis peak area integration at 215 nm after derivatization with Ac_2O. [c] Selectivity was determined by HPLC-UV/Vis peak area integration at 215 nm before derivatization with Ac_2O.

As anticipated, the phenolic acetyl group was not removed under the conditions used for hydrolysis of the oxazolidine **9a**. Diluting the mixture after a flow reaction with the same amount of 1 N HCl and subsequent heating for 20 min at 80 °C in a rotary evaporator (140 mbar) resulted in only 22% acetyl hydrolysis. For further preliminary hydrolysis reactions, the mixture after oxidation was diluted with the same amount of aqueous sulfuric acid and heated in a rotary

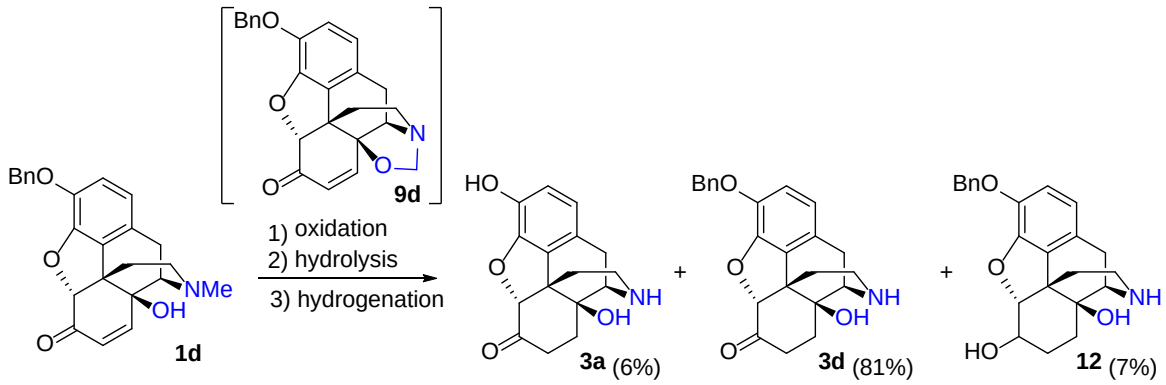
evaporator. An essentially complete hydrolysis was obtained after heating the reaction mixture with 8 M H_2SO_4 at 80 °C for 30 min. Unfortunately, 8-hydroxy-noroxymorphone **11**, the product from conjugate addition of water to the enone, formed in large amounts (up to ~30%; Scheme 5 and Scheme S2 in the Supporting Information).



Scheme 5. Oxidation of 14-hydroxymorphinone **1c** and subsequent hydrolysis.

To avoid the harsh reaction conditions during hydrolysis, reactions with 3-benzyl (Bn) protected 14-hydroxymorphinone were attempted. 3-Benzyl-14-hydroxymorphinone **1d** can be prepared in close to quantitative yields in a simple one-step literature procedure.[19] Flow oxidation reactions under the conditions described above, with 2.5 mol% $Pd(OAc)_2$ on scales from 0.6 g to 6 g, yielded consistent conversions of 97-98% after a residence time of around 20 min (Scheme 6). The selectivity for the oxazolidine **9d** was very high and hardly any side-products were detected according to HPLC and ^{1}H-NMR analysis (97% to 99% selectivity according to HPLC; see Figure S2 in the Supporting Information).

After the continuous flow oxidation, the same volume of 1N HCl was added to the crude reaction mixture and the sample was heated for 20 min at 80 °C in a rotary evaporator at 140 mbar. The resulting reaction mixture was directly pumped through the H-Cube Pro using a 10% Pd/C catalyst cartridge (30 °C, 30 bar H_2 pressure). HPLC-UV/Vis and HPLC-MS analysis revealed that the 3-Bn-14-hydroxynormorphinone **8d** was completely consumed. The main product was the 3-Bn-noroxymorphone **3d** (81%, Scheme 6). Additionally, significant amounts of the alcohol **12**, formed by hydrogenation of the ketone, were observed. Only 6% of the desired noroxymorphone **3a** were formed in this reaction (Scheme 6).



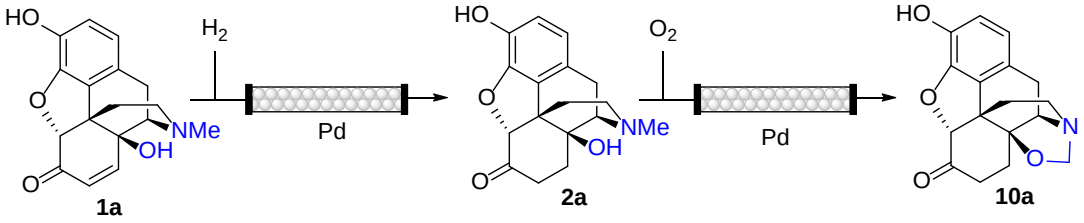
Scheme 6. Oxidation and hydrolysis of 3-Bn-14-hydroxymorphinone **1d** and subsequent hydrogenation.

Overreduction of the ketone is facilitated by the highly acidic conditions after hydrolysis. Thus, the product of a batch oxidation on a 0.34 mmol scale, and subsequent hydrolysis in the rotary evaporator, was isolated by precipitation with MeCN. Drying in a vacuum oven overnight at 50 °C afforded 110 mg of 3-Bn-14-hydroxynormorphinone **8d** in excellent purity (as the HCl salt). A sample of 100 mg of this product was dissolved in 10 mL MeOH and 28 mg of Pd/C (10 mol%) were added. The mixture was stirred for 4 hours at room temperature under an atmosphere of H_2 (balloon) and Pd/C was subsequently removed by filtration. Removing MeOH under reduced pressure afforded the noroxymorphone **3a** in high purity (75% yield, 2 steps; see Figure S3 in the Supporting Information).

2. Hydrogenation/demethylation sequence

2.1. Continuous flow oxidation in a packed bed reactor. Even though the final product was formed with excellent selectivity employing 3-benzyl-14-hydroxymorphinone **1d** as the starting material, the use of a protection group and the need to isolate the intermediate 3-Bn-14-hydroxynormorphinone **8d** reduces atom economy and increases process complexity. A sequence consisting of hydrogenation of 14-hydroxymorphinone **1a** to oxymorphone **2a** and subsequent *N*-demethylation to noroxymorphone **3a** could potentially allow the consecutive usage of the same palladium catalyst for both hydrogenation and oxidation. Furthermore, side-products arising from double bond hydration are avoided. We initially envisaged a process with two consecutive packed bed reactors. The concentrations of the mixtures were reduced to 0.1 M for the following reactions, to keep starting material and the corresponding oxazolidine in solution and, additionally, to reduce formation of side-products from oxidative dimerization. Hydrogenation of 14-hydroxymorphinone **1a** in the first packed bed reactor and oxidation in the second packed bed

reactor was expected to furnish oxazolidine **10a**, which can be directly hydrolyzed to the desired noroxymorphone **3a** (Scheme 7).



Scheme 7. Initially envisaged process for hydrogenation/oxidative cyclization sequence for the preparation of **10a** using heterogeneous catalysts.

For the initial experiments, hydrogenation of the 14-hydroxymorphone **1a** was carried out in DMA as solvent over Pd/C (Scheme 7). The resulting solution of oxymorphone **2a** was directly subjected to continuous flow oxidation using a fixed bed reactor setup similar to that described in Figure 1. As bed reactor a column (Omnifit®) filled with sol-gel entrapped SiliaCat DPP-Pd as heterogeneous catalyst was used. The catalyst consists of an organosilica matrix functionalized with diphenylphosphine ligands bound to Pd(II). SiliaCat DPP-Pd has been used for a wide range of Pd-catalyzed organic transformations,[20] and, importantly, has shown a high resistance against catalyst leaching for reactions involving both heterogeneous Pd(0) and homogeneous Pd(II) species in the reaction mechanism.[21]

Preliminary experiments were performed using a 0.7 mL packed bed reactor containing 220 mg of the immobilized catalyst (0.055 mmol Pd). As commercial Siliacat DPP-Pd is initially in a Pd(II) form, the catalyst was pre-activated by pumping a solution of isopropanol or ethylene glycol (EG) in DMA (50% vol) through the column at 120 ºC. During this process, a rapid change in the catalyst color from orange to black could be visually observed, indicating the transformation from Pd(II) to Pd(0) (Figure 3). Ultimately, ethylene glycol was selected as additive for the catalyst activation, as more reproducible results were obtained compared to *i*PrOH. When a solution of oxymorphone **2a** in DMA was processed using the packed bed reactor with the activated Pd catalyst (using a flow rate of 0.4 mL/min for the liquid phase, and 2.05 mL/min for O_2; 1.5 mol equiv of O_2) 30% conversion to the desired 1,3-oxazolidine **10a** was obtained at 120 °C (HPLC analysis, 205 nm). However, HPLC monitoring of the reaction output during a 5 mL run revealed a rapid decrease in the reaction conversion (see Figure S4 in Supporting Information). Moreover, the immobilized catalyst had partially recovered its initial orange coloration. After a fresh "catalyst activation" cycle using ethylene glycol in DMA at high

temperatures the oxidation could be repeated with identical results. This continuous flow oxidation/catalyst reactivation cycle could be repeated many times without an apparent drop in catalytic efficiency (see Figure S4 in the Supporting Information). We therefore ascribe the observed decrease in conversion in each cycle to the transformation of the immobilized Pd in the support to inactive Pd(II) species instead of leaching.

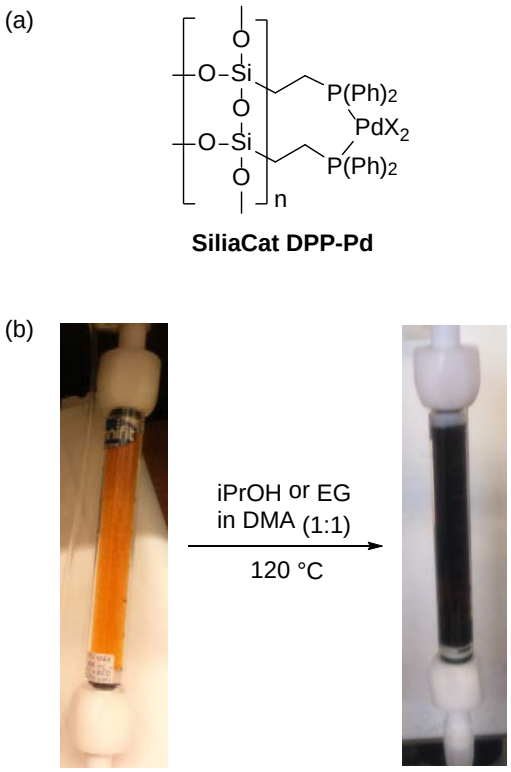


Figure 3. Structure of the SiliaCat DPP-Pd catalyst (a) and preactivation of the catalyst in the packed-bed reactor (b).

We next decided to use a larger packed bed reactor (2.4 mL volume, 760 mg SiliaCat DPP-Pd) to extend the residence time and improve the reaction conversion. Moreover, ethylene glycol was added as co-solvent directly to the reaction mixture to improve catalyst stability. Thus, the catalyst is reactivated concurrently with the reaction. With the larger packed-bed reactor, high conversions and excellent selectivities were obtained (Figure 4) and, importantly, improved catalyst stability. Using 10% EG in DMA as solvent system (Figure 4a) an initial conversion of 97% (HPLC area) with 98% selectivity was obtained. Only minor amounts of two side products were observed: the over-oxidized carboxamide **13** and the oxazolidine **9a** from a palladium-catalyzed aerobic dehydrogenation. No traces of the dimer from oxidative phenol coupling were detected in the crude reaction mixture (Figure S5 in the Supporting Information). A sample of 10

mL reaction volume was processed with a stable selectivity of 97-98%. The conversion dropped slightly to 93% over the course of the reaction. Increasing the amount of EG to 20% somewhat improved catalyst stability (Figure 4b). However, a slightly higher amount of carboxamide **13** was observed by HPLC monitoring, thus decreasing the reaction selectivity.

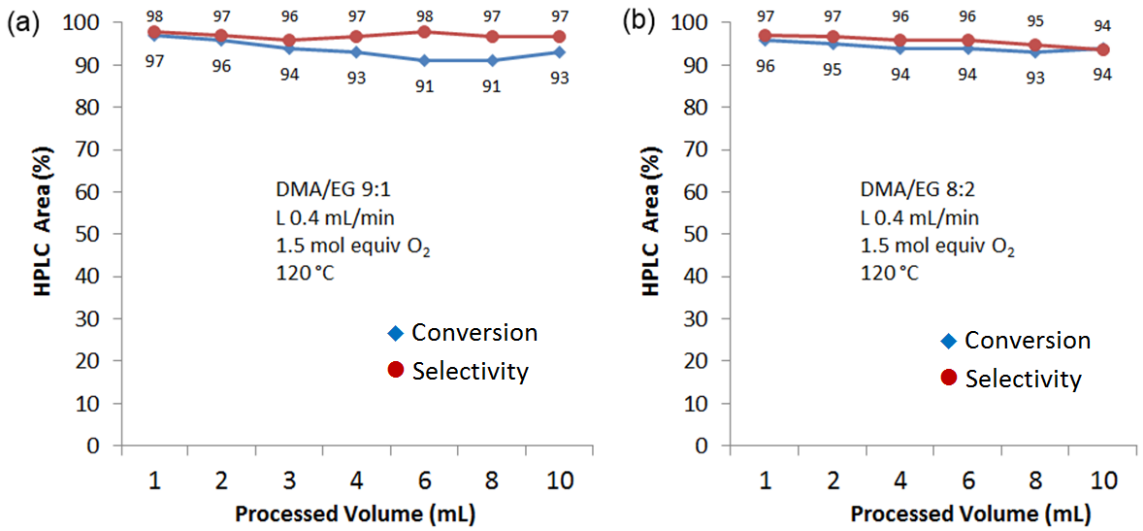


Figure 4. HPLC monitoring (205 nm) for the continuous flow oxidation of **2a** to **10a** using ethylene glycol as additive. (a) 10% EG in DMA; (b) 20% EG in DMA. 10 mL reaction volume was processed for each experiment.

An important advantage of this methodology is that there is no need of removing of the metal catalyst after the reaction. Thus, the reaction mixture collected from the output was simply concentrated under reduced pressure until ca. 20% of its initial volume, and after addition of cold water the desired oxazolidine **10a** crystallized in 68% yield.

To further evaluate the catalyst stability a longer run (50 mL) was performed using the same catalyst cartridge. HPLC monitoring of the crude reaction mixture revealed a gradual decrease in the reaction conversion (Figure 5), going below 90% after 15 mL had been processed. To assess whether the drop in catalytic efficiency was due to catalyst leaching from the solid support or inefficient reactivation of the Pd(0) by EG, the crude reaction mixture was analyzed by ICP-MS. The results revealed that the crude solution contained 46.4 ppm Pd, equating to a total amount of 2.1 mg of Pd leached from the solid support. This value corresponds to 10% of the initial total amount of Pd in the catalyst bed. These data clearly unveil that the metal does leach from the support during the oxidation of oxymorphone **2a** to **10a**. Even though the procedure presented herein appears to be very useful for small scale reactions, the scalability of the process

using this supported catalyst would certainly be problematic, and a process relying on a homogeneous Pd source may thus be preferable.

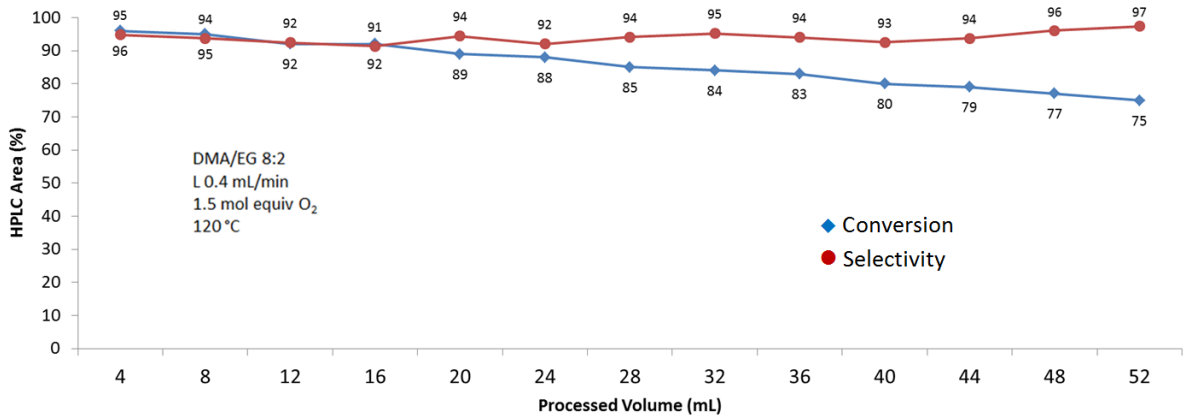


Figure 5. HPLC monitoring (205 nm) for the continuous flow oxidation of **2a** to **10a** during a 50 mL run.

2.2. Continuous flow oxidation in a gas-liquid tubular reactor. Additional continuous flow experiments were performed in a FEP tube reactor (Figure 2) with palladium(0) colloids (tube reactor: 1.6 mm inner diameter, 28 mL volume). For a typical experiment $Pd(OAc)_2$ (1-3 mol%) and AcOH were dissolved in DMA (5 mL). The solution was heated under stirring at 120°C for ca. 15 min, resulting in a dark mixture containing the colloidal Pd(0). Upon cooling, 14-hydroxymorphinone **1a** (1 mmol) was added and the mixture stirred under H_2 atmosphere to generate the oxymorphone **2a**. As expected, hydrogenation of 14-hydroxymorphinone **1a** to oxymorphone **2a** using the *in-situ* generated colloidal Pd(0) performed very well, and full conversion was observed after 1 hour at atmospheric pressure for catalyst loadings ranging from 1 mol% to 3 mol%. HPLC analysis of the reaction mixture confirmed a highly selective reduction of the double bond, with no traces of side products being observed. The reaction mixture was subsequently directly processed in the oxidation flow setup, introducing the homogeneous crude mixture to the reactor via a sample loop. Processing of the crude hydrogenation reaction mixture through the aerobic oxidation flow setup resulted in formation of the desired 1,3-oxazolidine derivative **10a** with good conversions and acceptable selectivity, demonstrating that the colloidal Pd(0) can be utilized both for the hydrogenation and oxidation step in an “one-pot” procedure (Figure S6 in the Supporting Information). Several reaction parameters were screened to obtain optimal reaction conditions for the oxidation step (Table S6 in the Supporting Information). The amount of AcOH used as additive had a significant influence on the conversion, the optimal

amount being 3 equivalents. Higher excess or smaller amounts clearly reduced the conversion. Notably, conversions above 90% were only achieved with catalyst loadings of 3 mol% after reaction times of approximately 20 to 30 minutes.

HPLC monitoring of the reaction sequence after the first and second step revealed that several side-products were formed during the oxidation, contributing to the moderate selectivity (80-90%) observed in most cases (Figure S6 in the Supporting Information). The main side products were identified as 1,3-oxazolidine **9a** (ca. 4% HPLC area), formed by palladium catalyzed aerobic dehydrogenation, and the dimer of **10a**, derived from oxidative phenol coupling (ca. 3% HPLC area). In an attempt to improve the selectivity for the formation of **10a**, reactions at lower temperatures were performed (80 °C to 100 °C). Thus, to obtain good conversions the reaction mixture was processed several times through the flow reactor. Notably, this strategy was unsuccessful and the reaction stopped after a number of passes in all cases (Figure S7 in the Supporting Information). These results support the hypothesis that the colloidal Pd(0) particles are deactivated in the presence of oxygen at high temperatures by the formation of an in-active Pd(II) species, such as $Pd(OAc)_2$.

A second possible source for the rather low activity of the catalyst in these reactions could be aggregation of the Pd(0) particles during the hydrogenation of **1a**. To test the catalytic activity of freshly generated colloidal Pd(0), continuous flow oxidation reactions were performed with the isolated oxymorphone **2a**. Colloidal palladium particles were generated from $Pd(OAc)_2$ in DMA/AcOH as described above, and the oxymorphone **2a** was dissolved into this solution. Gratifyingly, using this approach, 99% conversion and 94% selectivity for the oxazolidine **10a** were obtained after 20 min residence time at 100 °C (for a HPLC-UV/Vis chromatogram of the crude reaction mixture see Figure S8 in the Supporting Information). After concentration of the crude reaction mixture to ca. 20% of the initial volume and addition of cold water, oxazolidine **10a** crystallized in excellent purity and 77% product yield.

Conclusion

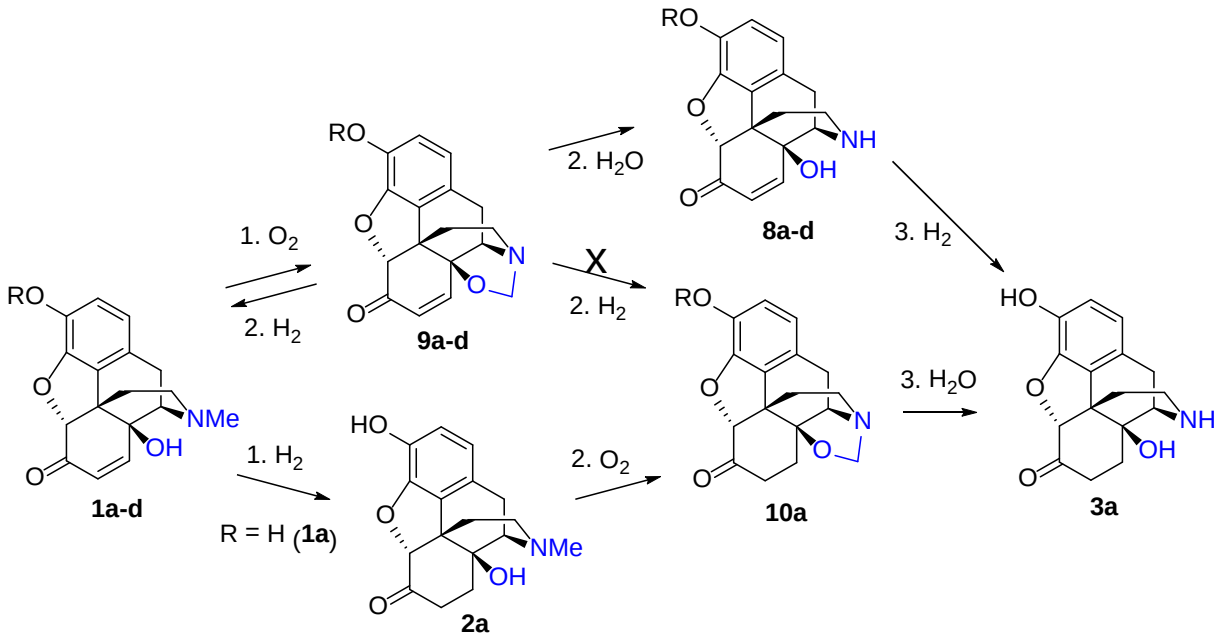
Herein we presented various strategies for the generation of noroxymorphone from 14-hydroxymorphinone. Noroxymorphone is the key intermediate in the synthesis of various opioid antagonists, including naloxone, naltrexone and nalmefene, as well as mixed agonists-antagonists like nalbuphine. The crucial reaction step towards generation of noroxymorphone is an aerobic *N*-methyl oxidation using palladium(0) as catalyst. Palladium(0) particles of high catalytic

activity were generated by heating $Pd(OAc)_2$ in DMA/AcOH. With the 14-hydroxy opioids dissolved in this solution, a quick and selective *N*-methyl oxidation to 1,3-oxazolidines ensues in the presence of O_2. The reaction consumes only O_2 as stoichiometric reagent and produces merely H_2O as by-product. Molecular oxygen is the cheapest, most abundant, and "greenest" oxidant. The deployment of catalytic processes with oxygen as terminal oxidant, instead of traditional processes based on stoichiometric oxidizing agents, offers significant potential to reduce waste emission. However, heating organic reagents and solvents with oxygen presents serious safety hazards, particularly on larger scale. These issues were addressed by developing a continuous flow process.

As the reaction sequence we initially envisaged to perform first the continuous flow *N*-methyl oxidation, followed by a direct continuous flow hydrogenation, utilizing the same palladium(0) catalyst for both transformations. This approach failed since C-O bond hydrogenolysis proceeded faster than C=C bond hydrogenation (Scheme 8). To avoid regeneration of the starting material, the 1,3-oxazolidine intermediate had to be hydrolyzed before the double bond hydrogenation (Scheme 8). Hydrolysis was performed under reduced pressure to avoid side-reactions with the released formaldehyde and to drive the reaction to completion under mild conditions. The palladium catalyst was partly lost during hydrolysis. The oxidation, hydrolysis, hydrogenation sequence yielded the desired noroxymorphone with good yield and purity. The main side-product was a dimer from oxidative coupling. Protection of the phenol moiety of 14-hydroxymorphinone increases stability towards oxidative coupling and improves solubility of the 1,3-oxazolidine. The removal of the phenol protecting group in the course of the following transformations demanded harsher reaction conditions in the respective reaction steps (Scheme 8).

Finally, a hydrogenation, oxidation sequence allowed employing the same palladium catalyst for both transformations, consuming only hydrogen and oxygen in the process (Scheme 8). However, the palladium(0) catalyst after hydrogenation had lower activity than freshly prepared catalyst, probably due to some aggregation of the palladium colloids. With freshly prepared palladium colloids, on the other hand, the oxidation of oxymorphone proceeded under particularly mild reaction conditions in the continuous flow reactor (100 °C, 20 min), and side-reactions, such as dehydrogenation to the enone or oxidative dimerization, were suppressed. Even though the reaction sequences presented herein appears to be clearly preferable to existing

synthesis routes, further analysis, including evaluation of potential towards optimization and life-cycle assessment, is needed to evaluate ecological-economic viability.



Scheme 8. Synthesis routes to noroxymorphone **3a**

Experimental Section

General remarks. ^{1}H-NMR spectra were recorded on a Bruker 300 MHz instrument. ^{13}C-NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q and m are used to indicate singlet, doublet, triplet, quadruplet and multiplet. Analytical HPLC-UV/Vis (Shimadzu LC20) analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 µm) at 37 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1 % TFA) and B (MeCN + 0.1 % TFA) at a flow rate of 1.5 mL/min (the following gradient was applied: linear increase from solution 3% B to 100 % B in 17 min). Low-resolution mass spectra were obtained on a Shimadzu LCMS-QP2020 instrument using electrospray ionization (ESI) in positive or negative mode. All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. The $Pd(OAc)_2$ was purchased from Aldrich (SKU: 683124).

ICP MS measurements. Liquid samples were diluted 1:100 and palladium was quantitatively determined at m/z 105 with an Agilent 7500ce inductively coupled plasma mass spectrometer. A

calibration was performed with an external calibration curve established from 1.000 g/L of Pd standard (CPI International). Indium served as the internal standard.

Analysis (see Scheme S1 in the Supporting Information). Method 1: Ac_2O derivatization: To a HPLC vial containing 1 mL of a saturated aqueous solution of $NaHCO_3$ were added 50 µL of the crude reaction mixture and 200 µL Ac_2O. The vial was capped, the septum perforated with a needle, and the mixture stirred vigorously at room temperature for 20 min. The content of the vial was then directly analyzed by HPLC-UV/Vis using the method described in the General Remarks section.

Method 2: Benzylbromide derivatization: 25 µL of benzyl bromide were added to 50 µL of the crude reaction mixture, and the sample was heated for 60 min at 70 °C. The sample was diluted with 1 mL MeCN and analyzed by HPLC-UV/Vis using the method described in the General Remarks section. The detection wavelength was set at 280 nm.

Method 3: 50 µL of the reaction mixture were diluted with 1 mL MeCN and the sample was analyzed by HPLC-MS. The respective m/z values were extracted from the total ion current chromatograms. The peak areas of the extracted-ion chromatograms were then used to calculate conversions of substrate to products.

Aerobic Oxidation under Batch Conditions. The reaction with 14-hydroxymorphinone **1a** on a 500 mg scale will serve as a representative procedure for batch oxidations: 18.7 mg of $Pd(OAc)_2$ (5 mol%) and 287 µL AcOH (3 equiv) were dissolved in 5 mL DMA. The mixture was heated for 10 to 20 min to 120 °C. A deep black solution of colloidal Pd(0) is obtained. 500 mg of the starting material were dissolved in this mixture, and the solution was again heated to 120 °C under vigorous stirring under an atmosphere of O_2 (balloon) or, alternatively, an atmosphere of air (open vessel). The reaction was stopped after HPLC analysis showed >95% conversion (see Analysis section). The reaction time depended on reaction scale but the reaction was generally completed after reaction times of 1 to 2 h. Alternatively, palladium(0) (e.g. Pd/C) can be directly used as catalyst in DMA or DMSO as solvent. The oxazolidine **9a**, derived from 14-hydroxymorphinone **1a**, precipitated from the mixture and can be isolated by simple filtration in high purity. Usually, the crude reaction mixtures after oxidation were directly used for further downstream reactions and no isolation was attempted.

Continuous-flow Oxidations in a Packed Bed Reactor (Figure 1). The flow reactor consisted of an HPLC pump for introducing the liquid feed (Uniqsis Pump Module). Oxygen gas from a gas cylinder was fed into the system via a mass flow controller (ThalesNano Gas Module or

Bronkhorst EL-Flow). The liquid and gaseous streams were combined in a T-mixer (stainless steel). The T-mixer was connected to the residence tube reactor via a fluoropolymer tubing (perfluoroalkoxy polymer (PFA), 1/16'' o.d., 0.8 mm i.d.). The PFA tubing allowed visual observation of the flow profile. The gas-liquid mixture then passed through the catalyst bed. As catalyst bed either pre-backed catalyst cartridges (ThalesNano CatCart®) or Omnifit® columns filled with the desired catalyst material were used. The processed reaction mixture finally left the system through an adjustable back pressure regulator (Swagelok (KCB1H0A2A5P60000, 0-26 bar) or Vapourtec (0-15 bar)). The oxidation of 14-hydroxycodeinone **1b** on a 100 mg scale will serve as a representative procedure for continuous flow reactions: DMA was pumped through the flow system at a flow rate of 0.3 mL/min and O_2 was introduced into the reactor with a flow rate of 5 mL_N/min (gas flow at normal conditions, *i.e.* T_n = 0 °C and p_n = 1 atm; 2.3 equivalents of O_2). The temperature of the coil heater was set to 120 °C. The pressure was adjusted to 20 bar. The substrate (100 mg) was dissolved in DMA (1 mL), and the resulting mixture was introduced into the injection loop. When the flow system was stable, the reaction mixture was pumped from the injection loop into the reactor. About 6 min after the reaction mixture was introduced into the reactor, the processed product solution left the system, was collected and analyzed.

Continuous-flow Oxidations under Gas-Liquid Biphasic Reaction Conditions (Figure 2). The flow reactor consisted of an HPLC pump for introducing the liquid feed (Uniqsis Pump Module). Oxygen gas from a gas cylinder was fed into the system via a mass flow controller (ThalesNano Gas Module or Bronkhorst EL-Flow). The liquid and gaseous streams were combined in a T-mixer (stainless steel). The T-mixer was connected to the residence tube reactor via a fluoropolymer tubing (perfluoroalkoxy polymer (PFA), 1/16'' o.d., 0.8 mm i.d.). The PFA tubing allowed visual observation of the flow profile. The residence coil reactor (fluorinated ethylene propylene (FEP), 1/8'' o.d., 1.6 mm i.d. 10, 28 or 57 mL) was heated in a GC oven to the desired temperature. The reaction mixture finally exited the system through a short cooling loop and a back-pressure regulator (either an adjustable back-pressure regulator: Swagelok (KCB1H0A2A5P60000, 0-26 bar) or Vapourtec (0-15 bar), or a static BPR from Upchurch Scientific). Pressure sensors were integrated into the T-mixer and directly after the pump. The oxidation of 14-hydroxymorphinone on a 600 mg scale will serve as a representative procedure for continuous flow reactions: DMA was pumped through the flow system at a flow rate of 1.0 mL/min and O_2 was introduced into the reactor with a flow rate of 10 mL_N/min (gas flow at normal conditions, *i.e.* T_n = 0 °C and p_n = 1 atm). The temperature of the GC-oven was set to 120

°C. The pressure was adjusted to 7 bar. The solution of colloidal palladium(0) was prepared by heating $Pd(OAc)_2$ (1.25 mol%) and acetic acid (3 equiv) in 9 mL DMA for 20 min at 140 °C. The substrate (600 mg) was dissolved in this mixture, and the mixture was introduced into the injection loop (14-hydroxymorphinone **1a** does not dissolve completely at this concentration in DMA at room temperature, but the solution becomes homogenous upon mild heating). When the flow system was stable, the reaction mixture was pumped from the injection loop into the reactor. 20 min after the reaction mixture was introduced into the reactor, the processed product solution left the system. The products were isolated as described above or were directly used for subsequent reactions. For reactions with 14-hydroxymorphinone **1a**, a quench solution of 1 N HCl was pumped into the reactor before the back-pressure regulator with a flow rate of 1 mL/min (Uniqsis Pump Module; Figure 2) and the reaction mixture was directly used for hydrolysis in a rotary evaporator.

(5aR,6R,8aS,8a^{1}S,11aR)-2-Hydroxy-5,5a-dihydro-7H-6,8a^1-ethanofuro[2',3',4',5':4,5]phenanthro[9,8a-d]oxazol-11(11aH)-one (9a): Starting material: 14-Hydroxymorphinone **1a** (batch reaction on a 500 mg scale). For isolation, the reaction mixture was cooled in an ice bath. The precipitate was separated by filtration and washed with cold water. Drying in a vacuum oven overnight provided 407 mg of the oxazolidine **9a** (82% yield). mp.: >300 °C (decomposition). ^{1}H NMR (300 MHz, DMSO) δ 9.28 (s, 1H), 6.79 (d, *J* = 10.1 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 6.18 (d, *J* = 10.1 Hz, 1H), 4.74 (d, *J* = 6.3 Hz, 1H), 4.73 (s, 1H), 4.60 (d, *J* = 5.5 Hz, 1H), 3.47 (d, *J* = 7.4 Hz, 1H), 3.23 (d, *J* = 18.8 Hz, 1H), 3.09 (dd, *J* = 18.9, 7.6 Hz, 1H), 2.82 – 2.65 (m, 2H), 2.34 – 2.23 (m, 1H), 1.37 (dd, *J* = 12.7, 3.3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 194.9, 148.3, 143.1, 139.5, 133.9, 130.6, 122.5, 120.3, 118.3, 87.3, 86.5, 73.4, 65.3, 47.9, 44.1, 33.1, 26.8. HRMS (APCI): m/z: calcd for $C_{17}H_{16}NO_4$ $[(M+H)]^+$: 298.107384, found: 298.107471.

(5aR,6R,8aS,8a^{1}S,11aR)-2-Methoxy-5,5a-dihydro-7H-6,8a^1-ethanofuro[2',3',4',5':4,5]phenanthro[9,8a-d]oxazol-11(11aH)-one (9b): Starting material: 14-Hydroxycodeinone **1b** (batch reaction on a 100 mg scale). The reaction mixture was extracted with $CHCl_3/H_2O$. Drying of the organic phase with $MgSO_4$ and evaporation of the solvent provided 94 mg of the crude oxazolidine **9b** (95% yield; contained some DMA; see the Supporting Information for ^{1}H-NMR).^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, J = 8.3 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.56 (d, *J* = 10.1 Hz, 1H), 6.23 (d, *J* = 10.1 Hz, 1H), 4.79 – 4.73 (m, 2H), 4.64 (s, 1H), 3.84 (s, 3H), 3.46 – 3.36 (m, 2H), 3.18 (dd, *J* = 19.1, 7.9 Hz, 1H), 2.88 – 2.80

(m, 2H), 2.35 (td, *J* = 12.3, 6.2 Hz, 1H), 1.61 (dd, *J* = 12.8, 4.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 145.8, 144.2, 142.7, 134.6, 130.0, 123.4, 120.0, 115.5, 87.6, 86.9, 73.6, 65.9, 56.8, 48.1, 32.8, 27.0. HRMS (APCI): m/z: calcd for $C_{18}H_{18}NO_4$ $[(M+H)]^+$: 312.123034, found: 312.122975.

(5aR,6R,8aS,8a1S,11aR)-2-(Benzyloxy)-5,5a-dihydro-7H-6,8a1-ethanofuro[2',3',4',5':4,5]phenanthro[9,8a-d]oxazol-11(11aH)-one (9d): Starting material: 3-Benzyl 14-hydroxycodeinone **1d** (flow reaction on a 600 mg scale). Evaporation of the solvent provided the crude oxazolidine **9d** in excellent purity (quant; contained some DMA; see the Supporting Information for ^{1}H-NMR).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.25 (m, 5H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.57 (d, *J* = 10.1 Hz, 1H), 6.24 (d, *J* = 10.1 Hz, 1H), 5.23 – 5.13 (m, 2H), 4.77 (q, *J* = 6.3 Hz, 2H), 4.68 (s, 1H), 3.47 – 3.36 (m, 2H), 3.17 (dd, *J* = 19.1, 7.9 Hz, 1H), 2.92 – 2.79 (m, 2H), 2.46 – 2.31 (m, 1H), 1.63 (dd, *J* = 12.8, 3.7 Hz, 1H).

Two Step *N*-demethylation: Oxidation and Subsequent Hydrolysis in a Rotary Evaporator (*cf.* Scheme 4). The reaction mixture from the oxidation reaction (see above) was diluted with the same amount of 1 N HCl. The mixture was then heated for 20 min at 80 °C in a rotary evaporator at 140 mbar. The phenolic acetyl group of **9c** was not removed under these conditions (see Scheme 5 and Scheme S2 in the Supporting Information for details).

14-Hydroxynormorphinone (8a): Starting material: 14-Hydroxymorphinone **1a** (500 mg). The mixture after oxidation and subsequent hydrolysis was diluted with 10 mL distilled water and brought to ~pH 9 with 25% aqueous ammonia. The precipitate was separated by filtration and washed with cold water. Drying in a vacuum oven overnight provided 468 mg of the crude 14-hydroxynormorphinone **8a** in good purity (98% yield; 93.5% purity according to HPLC-UV/Vis at 205 nm). ^{1}H NMR (300 MHz, DMSO) δ 6.85 (d, *J* = 10.1 Hz, 1H), 6.56 – 6.48 (m, 2H), 5.99 (d, *J* = 10.0 Hz, 1H), 4.57 (s, 1H), 3.07 (t, *J* = 3.6 Hz, 1H), 2.85 (d, *J* = 3.5 Hz, 2H), 2.66 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.42 (dd, *J* = 13.4, 3.5 Hz, 1H), 2.26 (td, *J* = 12.2, 5.0 Hz, 1H), 1.27 (dd, *J* = 12.1, 2.6 Hz, 1H).

3-Benzyl-14-hydroxynormorphinone (8d): Starting material: 3-Benzyl-14-hydroxymorphinone **1d** (138 mg). The product, after oxidation and subsequent hydrolysis, was precipitated with MeCN. Drying in a vacuum oven overnight at 50 °C afforded 110 mg of 3-Bn-14-hydroxynormorphinone **8d** (probably as the HCl salt; 75% yield). Alternatively, the product was isolated as the free base after diluting with 120 mL water and precipitation by neutralization with

aqueous 25% NH_3 (4.3 g from a 6 g experiment; 74%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.40 – 7.25 (m, 5H), 6.93 (d, *J* = 10.2 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.18 (d, *J* = 10.2 Hz, 1H), 5.15 (s, 2H), 4.87 (s, 1H), 3.99 (d, *J* = 4.1 Hz, 1H), 3.27-3.21 (m, 3H), 2.90 (td, *J* = 13.0, 3.8 Hz, 1H), 2.76 (td, *J* = 13.1, 4.7 Hz, 1H), 1.86 (dd, *J* = 13.0, 3.0 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 193.6, 146.4, 145.1, 141.9, 137.0, 133.1, 129.4, 128.0, 127.6, 127.5, 123.4, 120.2, 118.8, 86.3, 71.5, 65.9, 56.7, 46.2, 37.0, 27.5, 25.5.

Three Step *N*-demethylation/Hydrogenation (*cf.* Scheme 4): The reaction with 14-hydroxymorphinone **1a** on a 600 mg scale will serve as a representative procedure: The homogenous solution after oxidation and subsequent hydrolysis in a rotary evaporator (see above) was directly pumped through the H-Cube Pro instrument (10% Pd/C catalyst cartridge; 0.4 mL/min flow rate; 25 °C reaction temperature; 30 bar). 1.5 min after the feed was switched from solvent (DMA) to reaction mixture, the product was collected (first product appeared after about 5.5 min). The solution was concentrated in vacuum to around 6 mL. Afterwards the mixture was diluted with 18 mL distilled water and brought to ~pH 9 with 25% aqueous ammonia. The precipitate was separated by filtration and washed with cold water. Drying in a vacuum oven overnight provided 403 mg of the crude noroxymorphone **3a** in good purity (70% yield, 92.8% purity according to HPLC-UV/Vis at 205 nm). The corresponding oxidation/hydrogenation with Bn-14-hydroxymorphinone **1d** (Scheme 6) gave incomplete removal of the protection group and partly hydrogenation of the carbonyl group (10% Pd/C catalyst cartridge; 0.4 mL/min flow rate; 30 °C reaction temperature; 30 bar).

Noroxymorphone (*3a*): ^{1}H NMR (300 MHz, DMSO) δ 6.56 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 4.67 (s, 1H), 2.98 – 2.82 (m, 4H), 2.64 – 2.56 (m, 1H), 2.42 – 2.21 (m, 2H), 2.11 – 2.02 (m, 1H), 1.77 – 1.67 (m, 1H), 1.41 (td, *J* = 14.2, 3.4 Hz, 1H), 1.14 (d, *J* = 11.4 Hz, 1H).

Preparation of Oxymorphone (2a). A suspension of 14-hydroxymorphinone (**1a**) (750 mg, 2.5 mmol) and 10% Pd/C (25 mg, 1 mol%) in DMA was stirred under an H_2 atmosphere for 1 h. Then, the reaction mixture was filtered using a syringe filter (PTFE, 0.45 μm) and the filtrate evaporated under reduced pressure.

Sequential Hydrogenation and Continuous-flow Oxidations in a Packed Bed Reactor (Scheme 7). A suspension of 14-hydroxymorphinone **1a** (150 mg, 0.5 mmol) and 10% Pd/C (10 mg, 1 mol%) in 5 mL od DMA/ethylene glycol 9:1 was stirred at room temperature under H_2 atmosphere for one hour. The mixture was filtered (0.45 μm pore size filter) and the clear solution was introduced into the flow reactor via an injection loop. The flow reactor had been

stabilized by pumping DMA/ethylene glycol 8:2 at a flow rate of 0.4 mL/min and O_2 with a flow rate of 2.05 mL/min (gas flow at normal conditions, i.e. T_N = 0 °C and p_N = 1 atm). The temperature of the packed-bed reactor (Omnifit® column) had been set to 120 °C and the pressure adjusted to 5 bar. After a residence time of approximately 20 min the processed product solution left the system. The reaction mixture collected from the reactor output was evaporated under reduced pressure until ca. 20% of the initial volume. 10 mL of cold water were added, and the solid obtained filtered and dried under vacuum at 50 °C (102 mg, 68%).

Sequential Hydrogenation and Continuous-flow Oxidations under Gas-Liquid Biphasic Reaction Conditions. $Pd(OAc)_2$ (3 mol%) and AcOH (3 equiv) were dissolved in DMA (5 mL) and placed in a 25 mL two-necked round-bottom flask. The mixture was heated at 120 °C for 15 min. Formation of Pd(0) could be visually observed. Upon cooling, 14-hydroxymorphinone (150 mg, 0.5 mmol) was added and the mixture stirred under H_2 atmosphere for 1 h. Then, the crude reaction mixture was introduced into the flow reactor via an injection loop. The flow reactor had been stabilized by pumping DMA at a flow rate of 0.75 mL/min and O_2 with a flow rate of 1.7 mL/min (gas flow at normal conditions, i.e. T_N = 0 °C and p_N = 1 atm). The temperature of the GC-oven had been set to 120 °C and the pressure adjusted to 5 bar. After a residence time of approximately 20 min the processed product solution left the system. The reaction mixture collected from the reactor output was evaporated under reduced pressure until ca. 20% of the initial volume. 10 mL of cold water were added, and the solid obtained filtered and dried under vacuum at 50 °C (115 mg, 77%).

(5a*R*,6*R*,8a*S*,8a^1*S*,11a*R*)-2-hydroxy-5,5a,9,10-tetrahydro-7*H*-6,8a^1-ethanofuro [2',3',4',5':4,5]phenanthro[9,8a-*d*]oxazol-11(11a*H*)-one *(10a)*: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.24 (s, 1H), 6.60 (q, *J* = 8.1 Hz, 2H), 4.87 (s, 1H), 4.61 (dd, *J* = 32.1, 5.5 Hz, 2H), 3.25 – 3.06 (m, 3H), 2.91 – 2.55 (m, 3H), 2.38 – 2.24 (m, 1H), 2.20 (dt, = 7.3, 4.0 Hz, 1H), 1.89 (dt, *J* = 7.3, 4.0 Hz, 1H); 1.47 (td, J = 14.8, 2.9 Hz, 1H), 1.25 (dd, J = 12.4, 4.0 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 208.2, 143.6, 139.7, 129.7, 122.1, 120.0, 118.1, 90.5, 86.1, 77.1, 63.6, 52.5, 44.1, 37.3, 34.4, 30.5, 26.6.

Acknowledgements

We thank Dr. W. Gössler (Uni Graz) for ICP MS measurements. We acknowledge support from ThalesNano Inc. for providing the catalyst cartridges. We are grateful to Dr. Doris Dallinger for proofreading the manuscript.

References

[1] (a) D. Kim, K. S. Irwin, K. Khoshnood, *Am. J. Public Health*, **2009**, *99*, 402-407; b) R. C. Dart, H. L. Surratt, T. J. Cicero, M. W. Parrino, S. G. Severtson, B. Bucher-Bartelson, J. L. Green, *N. Engl. J. Med.* **2015**, *372*, 241-248.

[2] B. Halfort, *Chem. Eng. News* **2016**, *94(20)*, 34-38.

[3] a) S. Hosztafi, C. Simon, S. Makleit, *Synth. Commun*. **1992**, *22*, 1673-1682; b) H. Yu, T. Prisinzano, C. M. Dersch, J. Marcus, R. B. Rothman, A. E. Jacobson, K. C. Ricea, *Bioorg. Med. Chem. Lett*. **2002**, *12*, 165-168; c) B. R. Selfridge, X. Wang, Y. Zhang, H. Yin, P. M. Grace, L. R. Watkins, A. E. Jacobson, K. C. Rice, *J. Med. Chem*. **2015**, *58*, 5038-5052; d) J. Marton, S. Miklòs, S. Hosztafi, S. Makleit, *Synth. Commun*. **1995**, *25*, 829-848; e) H. S. Park, H. Y. Lee, Y. H. Kim, J. K. Park, E. E. Zvartauc, H. Lee, *Bioorg. Med. Chem. Lett*. **2006**, *16*, 3609-3613.

[4] a) P. X. Wang, T. Jiang, G. L. Cantrell, D. W. Berberich, B. N. Trawick, T. Osiek, S. Liao, F. W. Moser, J. P. McClurg (Mallinckrodt Inc.), US20090156818A1, 2009; b) P. X. Wang, T. Jiang, G. L. Cantrell, D. W. Berberich, B. N. Trawick, S. Liao (Mallinckrodt Inc.), US 20090156820A1, 2009; c) S. Hosztafi, S. Makleit, *Synth. Commun.* **1994**, *24*, 3031-3045; (d) A. Ninan, M. Sainsbury, *Tetrahedron* **1992**, *48*, 6709-6716.

[5] a) M. Ann, A. Endoma-Arias, D. P. Cox, T. Hudlicky, *Adv. Synth. Catal*. **2013**, *355*, 1869-1873; b) G. Kok, T. D. Asten, P. J. Scammells, *Adv. Synth. Catal*. **2009**, *351*, 283-286; c) Z. Dong, P. J. Scammells, *J. Org. Chem*. **2007**, *72*, 9881-9885; d) T. Rosenau, A. Hofinger, A. Potthast, P. Kosma, *Org. Lett*. **2004**, *6*, 541-544; e) D. D. D. Pham, G. F. Kelso, Y. Yang, M. T. W. Hearn, *Green Chem*. **2012**, *14*, 1189-1195; f) D. D. D. Pham, G. F. Kelso, Y. Yang, M. T. W. Hearn, *Green Chem*. **2014**, *16*, 1399-1409; g) Y. Li, L. Ma, F. Jia, Z. Li, *J. Org. Chem*. **2013**, *78*, 5638-5646.

[6] R. J. Carroll, H. Leisch, E. Scocchera, T. Hudlicky, D. P. Cox, *Adv. Synth. Catal*. **2008**, *350*, 2984-2992.

[7] A. Machara, L. Werner, M. A. Endoma-Arias, D. P. Cox, T. Hudlicky, *Adv. Synth. Catal.* **2012**, *354*, 613-626.

[8] A. Machara, D. P. Cox, T. Hudlicky, *Adv. Synth. Catal*. **2012**, *354*, 2713-2718.

[9] S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan, D. H. B. Ripin, *Chem. Rev*. **2006**, *106*, 2943-2989

[10] B. Gutmann, P. Elsner, D. P. Cox, U. Weigl, D. M. Roberge, C. O. Kappe, *ACS Sust. Chem. Eng.* **2016**, *4*, 6048−6061.

[11] For recent selected reviews on flow chemistry, see: a) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev*. **2016**, *45*, 4892-4928; b) C. Wiles, P. Watts, *Green Chem*. **2014**, *16*, 55-62; c) S. V. Ley, D. E. Fitzpatrick, R. J. Ingham, R. M. Myers, *Angew. Chem., Int. Ed*. **2015**, *54*, 3449-3464; d) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem., Int. Ed*. **2015**, *54*, 6688-6728.

[12] a) A. Gavriilidis, A. Constantinou, K. Hellgardt, K. K. Hii, G. J. Hutchings, G. L. Brett, S. Kuhn and S. P. Marsden, *React. Chem. Eng.* 2016, 1, DOI: 10.1039/C6RE00155F; b) H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque and T. Noël, *Chem. Soc. Rev*. **2016**, *45*, 83-117; c) B. Pieber, C. O. Kappe, *Top. Organometal. Chem*. **2016**, *57*, 97–136; d) C. Hone, D. Roberge, C. O. Kappe, *ChemSusChem* **2016**, *9*, DOI: 10.1002/cssc.201601321.

[13] For a preliminary communication, see: B. Gutmann, U. Weigl, D. P. Cox, C. O. Kappe, *Chem. Eur. J.* **2016**, *22*, 10393-10398.

[14] a) L. Werner, M. Wernerova, A. Machara, M. A. Endoma-Arias, J. Duchek, D. R. Adams, D. P. Cox, T. Hudlicky, *Adv. Synth. Catal.* **2012**, *354*, 2706-2712; b) M. A. Endoma-Arias, D. P. Cox, T. Hudlicky, *Adv. Synth. Catal.* **2013**, *355*, 1869-1873.

[15] J. G. de Vries, *Dalton Trans.* **2006**, 421-429.

[16] The color change associated with oligomerization of opiates and other alkaloids in a mixture of formaldehyde and acid is used as a simple method for drug identification (Marquis reagent). C. L. O'Neal, D. J. Crouch, A. A. Fatah, *Forensic Sci. Int.* **2000**, *109*, 189-201.

[17] a) M. Irfan, T. N. Glasnov, C. O. Kappe, *ChemSusChem* **2011**, *4*, 300-316; b) P. J. Cossar, L. Hizartzidis, M. I. Simone, A. McCluskey, C. P. Gordon, *Org. Biomol. Chem*. **2015**, *13*, 7119-7130.

[18] Methods and technologies to handle solids in continuous flow reactors are under active development. For selected reference on this topic, see: a) R. L. Hartman, *Org. Process Res.*

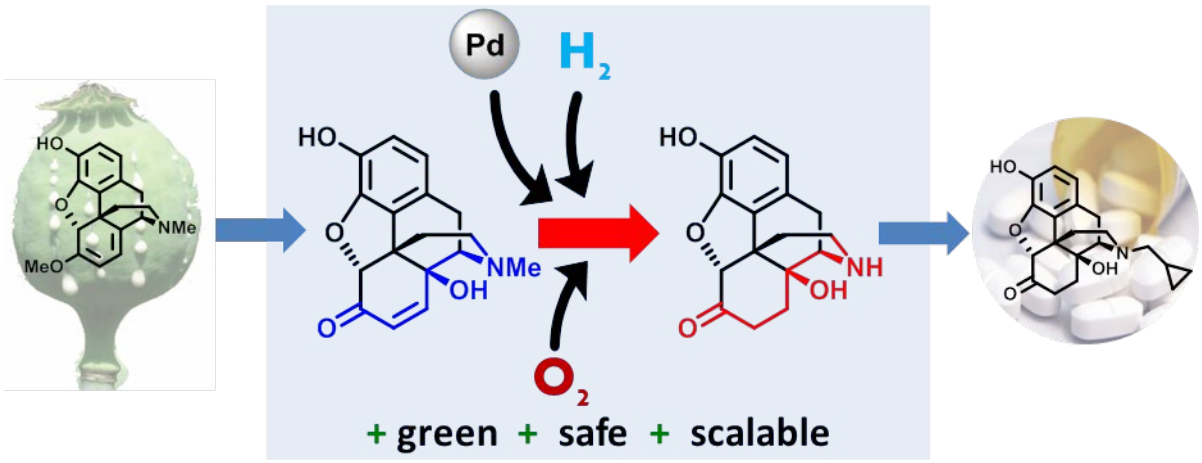
Dev. **2012**, *16*, 870−887; b) Y. Chen, J. C. Sabio, R. L. Hartman, *J. Flow. Chem.* **2015**, *5*, 166−171.

[19] H. Schmidhammer (University of Innsbruck), Process for the production of 14-oxygenated morphinan-6-one, WO2012013671A1, 2012.

[20] R. Ciriminna, V. Pandarus, A. Fidalgo, L. M. Ilharco, F. Béland, M. Pagliaro, *Org. Process Res. Dev*. **2015**, *19*, 755-768.

[21] R. Greco, W. Goessler, D. Cantillo, C. O. Kappe, *ACS Catal*. **2015**, *5*, 1303-1312.

TOC Graphic



The generation of noroxymorphone from 14-hydroxymorphinone by *N*-demethylation/hydrogenation was explored. The crucial reaction step was a continuous flow *N*-methyl oxidation with colloidal palladium(0) as catalyst and pure oxygen as stoichiometric oxidant.

Keywords: oxygen; palladium; microreactors; flow chemistry; *N*-demethylation; naltrexone; naloxone

Key Topic: Flow Chemistry