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Mg-Catalyzed OPPenauer Oxidation—Application to the Flow Synthesis of a Natural Pheromone

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Abstract: The so-called OPPenauer oxidation is well known for its ability to oxidize valuable alcohols into their corresponding aldehydes or ketones. In particular, it has proven to be extremely successful in the oxidation of sterols. On the other hand, its application—in the original formulation—to the obtainment of ketones outside the field of steroids met a more limited success because of less favorable thermodynamics and side reactions. To circumvent these issues, the first example of magnesium-catalyzed OPPenauer oxidation is described. The oxidation of primary and secondary alcohol was performed using pivaldehyde or bromaldehyde as the oxidant and cheap magnesium *tert*-butoxide as catalyst. Decent to excellent yields were obtained using reasonable catalytic charge. The synthesis of a pheromone stemming from the *Rhynchophorus ferrugineus* was obtained by tandem addition-oxidation of 2-methylpentanal and the process was successfully applied to continuous flow on a multigram scale.

Keywords: Oppenauer oxidation; magnesium; catalysis; alcohols; aldehydes; ketones; pheromone; *Rhynchophorus ferrugineus*

1. Introduction

OPPenauer (OPP) oxidation [1], the reverse process of the Meerwein-Ponndorf-Verley (MPV) reduction [2,3] is a classical, well known yet useful method. Indeed, alcohol oxidation to carbonyl constitutes one of the most important transformations in organic chemistry. However, despite the first initial success of the OPP oxidation procedure in the oxidation of steroidal compounds, it did not find widespread utility in the organic chemistry field outside of a few tuned and very specific natural product syntheses [4–9]. This is mostly because over-stoichiometric amounts of aluminum reagents were required to achieve good yields under reasonable reaction conditions [10–15]. To overcome this sluggish activity, some typical procedures involving a broad range of organic oxidizing reagents and metal-based systems have emerged. Simple salts as K [16,17] and Na [18,19] were first used in respectively stoichiometric and catalytic quantities to promote the OPP oxidation while more complex metal-based systems rapidly arose. Most of them were involving transition metals such as Ru [20,21], Ir [22,23], Fe [24], Zr [25] or more recently Mn [26], used in catalytic amounts but also other elements such as In [27,28], or Si [29]. These advances have contributed to the re-emergence of the OPP oxidation as an attractive process. Nevertheless, all these procedures have disadvantages; they rely on expensive metal complexes and/or elevated temperatures, are often toxic and eventually generate noxious wastes. Among these metals, magnesium appears to be an extremely attractive candidate as it possesses many properties appealing in catalysis such as low cost, high abundance, large possibilities of coordination and easy treatment of the resulting salts.

The Mg-OPP oxidation was first explored as a stoichiometric process in 1987 by Brian Byrne et al. using excess of magnesium under the form of Grignards [30], followed by numerous Knochel's protocols which were considered to be the most advantageous as the *in situ* formed magnesium alkoxides are intrinsically powerful promoters for the forthcoming hydride transfer [31–33]. Nevertheless, Grignard reagents should be accurately titrated beforehand and transferred carefully in case over- or less-loading will lead to significant side reactions such as Aldol condensation and Tishchenko esterifications [34]. Additionally, routes starting from Grignard reagents demand low reaction temperatures, and sensitive functional groups are still found difficult to tolerate [35]. To circumvent these problems, we believe that a magnesium catalyzed variant of the well-known OPP oxidation could be a good way to promote a more effective system to oxidize alcohols into carbonyls without the disagreement of the other systems.

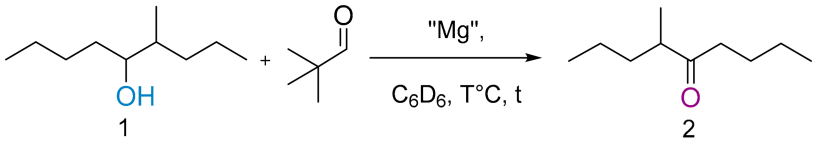
2. Results and Discussions

The oxidation of ferrugineol (**1**) (see Figure S1), to give the corresponding ketone ferrugineone (**2**) was chosen to be our model substrate (see Figure S2). Indeed, this secondary alcohol is challenging since it is sterically hindered, non-conjugated, and not easily enolizable; however, it can lead to elimination reactions in basic medium which would give the corresponding alkene.

2.1. Preliminary Tests

Pivaldehyde [14] was selected as the first hydride acceptor owing to its low dielectric constant and high oxidation potential (E_0 = 211 mV) [19]. Different magnesium oxides and a magnesium salt were studied to see if the OPP oxidation could be performed with catalytic amounts of these species (Table 1).

Table 1. Screening of conditions for the Mg-catalyzed oxidation of ferrugineol (**1**) to ferrugineone (**2**).



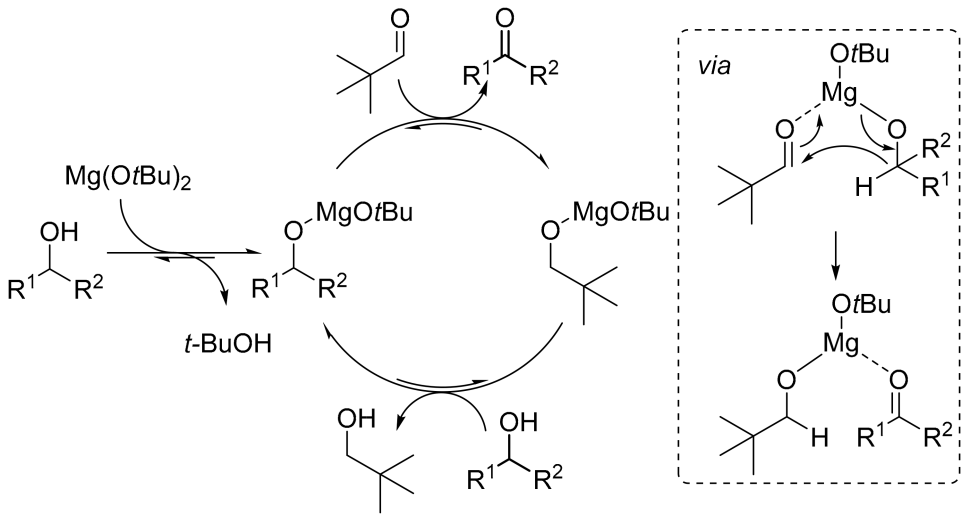
Entry	"Mg" (equiv)	Temperature (°C)	Time (h)	^{1}H NMR (%) Conversion
entry 1	$MgCl_2$ (0.4)	100	3	3
entry 2	$Mg(OH)_2$ (0.4)	100	3	2
entry 3	$Mg(OEt)_2$ (0.4)	100	3	31
entry 4	$Mg(OEt)_2$ (0.4)	100	6	33
entry 5	MgO (0.4)	100	3	2
entry 6	**$Mg(OtBu)_2$ (0.3)**	**110**	**1**	**70**
entry 7	$Mg(OtBu)_2$ (0.3)	60	1	21
entry 8	$Mg(OtBu)_2$ (0.3)	60	3	32

Reaction conditions: ferrugineol (1.0 equiv; 0.63 mmol), pivaldehyde (2.0 equiv), Mg catalyst (0.3 or 0.4 equiv), C_6D_6 (400 µL) under nitrogen. Note: Every bold used in tables highlight the best result.

Different catalytic charges were tested in deuterated benzene to evaluate the reaction efficiency via NMR conversions. It clearly appeared that $MgCl_2$, $Mg(OH)_2$ and MgO as catalysts were not the best candidates given that 3% conversion was the maximum obtained after 3 h heating (Table 1, entries 1, 2 and 5, Figures S3, S4 and S7).

$Mg(OEt)_2$ gave average conversions (Table 1, entries 3 and 4, Figures S5 and S6) whereas magnesium *tert*-butoxide appeared to be the most effective to catalyze the reaction (entry 6, Figures S8 and S9). It is noteworthy that the resulting *t*BuOH cannot be oxidized therefore limiting side reactions (Figures S10, S11, S12 and S13). Reasonable NMR conversion was observed (70%) after only an hour 30% catalyst with a slight aldehyde excess at 110 °C. It seems likely that the reaction proceeds through

deprotonation, alcoholate-adduct formation via hydride transfer followed by classical OPP oxidation (Scheme 1).



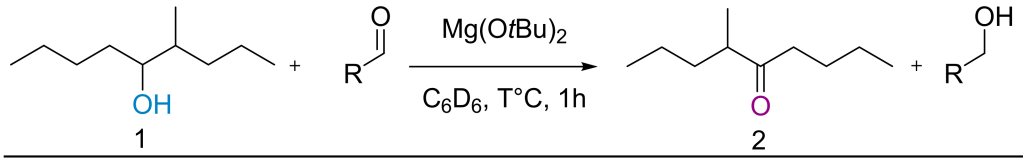
Scheme 1. Proposed mechanism for the Mg-catalyzed OPP oxidation.

2.2. Optimization of the Reaction Conditions

2.2.1. Aldehyde and Temperature Studies

Magnesium *tert*-butoxide was thus chosen as the magnesium source whereas the aldehyde, the solvent and temperature, and the alcohol nature were studied. Pivaldehyde was first chosen as the hydride acceptor as described earlier but the influence of the aldehyde's nature was also studied (Table 2, entries 1 to 5). 2-methylpentanal and isobutyraldehyde are inexpensive, enolizable, yet sterically hindered aldehydes preventing from side reaction. They both led to low conversions, respectively 21 and 25% (Table 2, entries 2 and 3). Pivaldehyde and bromaldehyde were more efficient than most of the other aldehydes (Table 2, entries 1 and 5) with respectively 70 and 84% conversions after only one hour heating so they were both further studied.

Table 2. Aldehydes tests results.



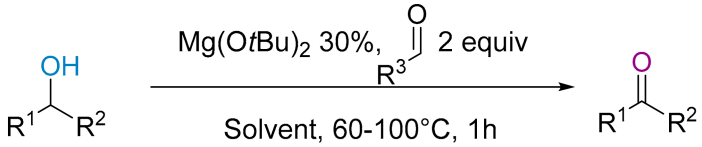
Entry	Aldehyde	Temperature (°C)	^{1}H NMR (%) Conversions [1]
entry 1	**Pivaldehyde**	**110**	**70**
entry 2	2-methylpentanal	60	21
entry 3	isobutyraldehyde	100	25
entry 4	Cyclohexane carboxaldehyde	100	54
entry 5	**Bromaldehyde**	**100**	**84**

Reaction conditions: ferrugineol (1.0 equiv; 0.63 mmol), aldehyde (2.0 equiv), Mg (0.3 equiv), C_6D_6 (400 µL) under nitrogen. [1] Conversions are calculated according to the starting material consumption related to the appearance of product. Note: Every bold used in tables highlight the best result.

2.2.2. Solvent Optimization

The optimal conditions of solvent and temperature were found by testing the oxidation of both ferrugineol and cyclohexanol as they are illustrating different types of substrate (Table 3). Unsurprisingly, considering the preliminary results in C_6D_6, non-polar, non-protic solvents such as toluene led to the best results (up to 71%). Interestingly, undistilled solvent were giving higher conversions than the distilled ones (Table 3, entries 4, 7 and 8), meaning that the presence of water could have an influence on the reaction efficiency. Known quantities of water (0.5 to 2.0 equiv) were then added to dry C_6D_6 to study this influence but it actually conducted to lower conversions (Table 3, entries 12 to 14). Further measurement of water trace amounts in both non-distilled C_6D_6 and toluene using a Karl Fisher metrohm were also performed. Indeed, adding 0.5 to 2.0 equiv of water actually meant 5.7 to 22 mg while we found that there were only 1.1 ppm (4.9×10^{-4} equiv) and 1.9 ppm (8.4×10^{-4} equiv) of water in 400 µL of respectively C_6D_6 and toluene. These values tell that traces amount of water are enough to increase the reaction conversion (probably involving the establishment of hydrogen bonds) whereas too much water would actually be unfavorable. Knowing that, the optimized reaction conditions were fixed with 30 mol% $Mg(OtBu)_2$, 2.0 equiv of pivaldehyde in C_6D_6 or toluene, according to the scale, for 1 h at 80 °C.

Table 3. Solvent optimization results.



Entry	Alcohol	Aldehyde	Solvent	^{1}H NMR (%) Conversions [1]
entry 1	Ferrugineol	Pivaldehyde	C_6D_6 [a]	70
entry 2	Ferrugineol	Pivaldehyde	Toluene [b]	54
entry 3	Ferrugineol	Pivaldehyde	DMF [b]	16
entry 4	Ferrugineol	Pivaldehyde	THF [b]	3
entry 5	Ferrugineol	Pivaldehyde	MeTHF [b]	16
entry 6	Ferrugineol	Pivaldehyde	DME [b]	traces
entry 7	Cyclohexanol	Pivaldehyde	C_6D_6 [b]	62
entry 8	**Cyclohexanol**	**Pivaldehyde**	**Toluene [c]**	**71**
entry 9	Cyclohexanol	Pivaldehyde	Dry Toluene [c]	46
entry 10	Cyclohexanol	Pivaldehyde	DCE [c]	55
entry 11	Cyclohexanol	Pivaldehyde	MTBE [c]	57
entry 12	Cyclohexanol	Bromaldehyde	C_6D_6 [d]	60
entry 13	Cyclohexanol	Bromaldehyde	Dry C_6D_6 [d]	31
entry 14	Cyclohexanol	Bromaldehyde	Dry C_6D_6 + H_2O [d]	traces
entry 15	Cyclohexanol	Bromaldehyde	Toluene [c]	45
entry 16	Cyclohexanol	Bromaldehyde	DCE [c]	36
entry 17	Cyclohexanol	Bromaldehyde	MTBE [c]	38
entry 18	Cyclohexanol	Bromaldehyde	Dry THF [c]	3
entry 19	Cyclohexanol	Bromaldehyde	Dry DCM [d]	39
entry 10	Cyclohexanol	Bromaldehyde	Dry Toluene [d]	49

Reaction conditions: alcohol (1.0 equiv), aldehyde (2.0 equiv), Mg catalyst (0.3 equiv), heating 1 h under nitrogen. [a] 110 °C, [b] 100 °C, [c] 80 °C, [d] 60 °C. [1] Conversions are calculated according to the alcohol consumption.

To demonstrate the generality and scope of this protocol we applied our conditions to different types of alcohols for the preparation of aromatic, aliphatic and α-β-saturated ketones (Figure 1).

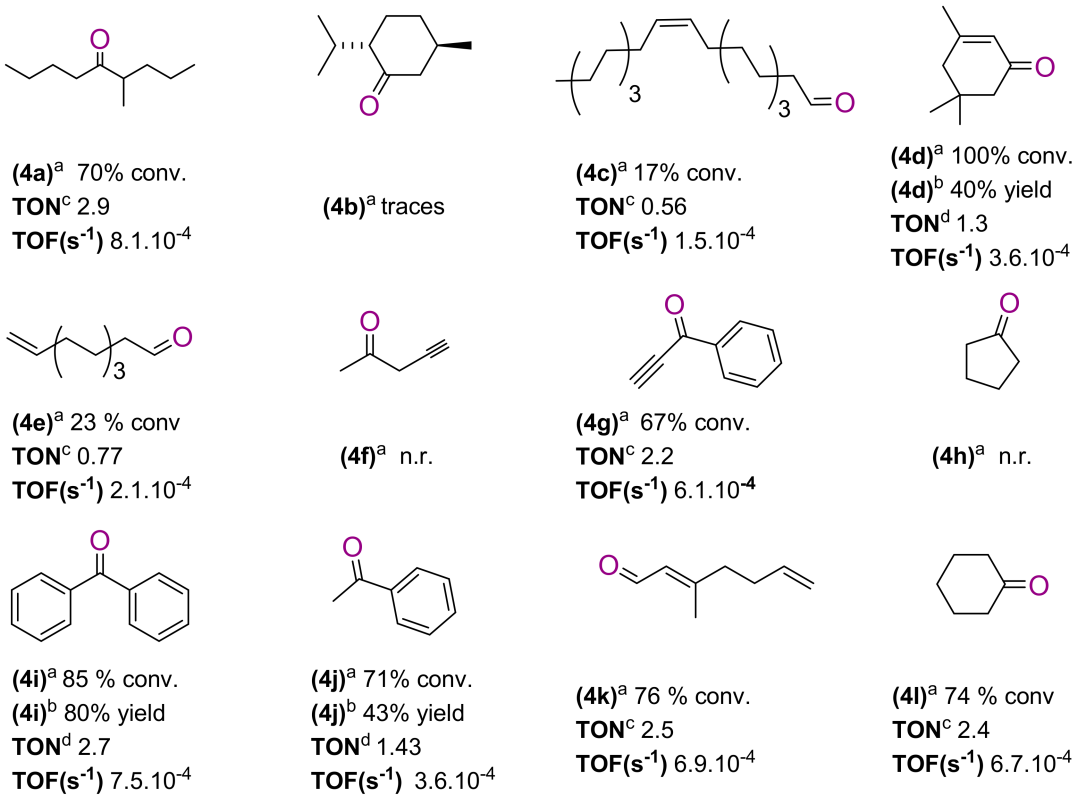


Figure 1. Results for the Mg-catalyzed OPP oxidation of various ketones. General Reaction conditions: Alcohol (**3a**) to (**3l**) (1.0 equiv), $Mg(OtBu)_2$ (0.3 equiv), aldehyde (2.0 equiv) [a] Procedure A; results reported as NMR conversions based on the starting alcohol. [b] Procedure B; results reported as isolated yields after column chromatography on silica gel. [c] TON (turn over number) and TOF (turn over frequency) were calculated using conversion values. [d] TON and TOF were calculated using isolated yields values.

2.3. Batch Applications

Alcohols were oxidized into their corresponding ketones with decent to high conversions (up to 100%, with a TON of 3.3). When the *ortho* position was too hindered (**4b**) or involved in a strained cycle (**4h**) the product was only observed as traces. Reaction was also limited by poor solubility (**4c**) or high volatility of the product, sometimes lost during isolation (**4f**). Subsequent transformation of the resulting products as hydrazones for low boiling points products was attempted but did not helped for any isolation. A direct distillation from the reaction mixture could be envisioned as an alternative. **4d** and **4i** were isolated after purification via column chromatography on silica gel.

Overall, despite some limitations, this Mg-catalyzed method proved to be efficient on different substrates.

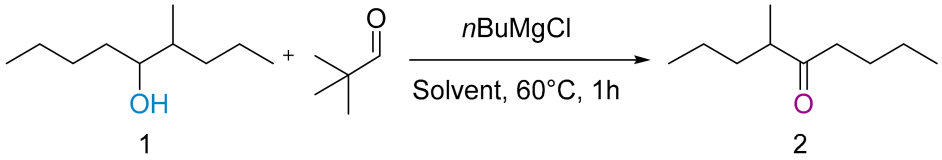
2.4. Flow Application

2.4.1. Using *n*BuMgCl in Catalytic Amounts

One of the objectives of developing this procedure was to synthesize ferrugineone starting from the corresponding alcohol ferrugineol. These natural pheromones from the Red Palm Weevil (*Rhynchophorus ferrugineus)* are both used in biocontrol [36,37]. The sexual confusion applications require a 90/10 mixture of ferrugineol and ferrugineone [38]. We envisioned preparing such a mixture by tandem addition—oxidation using 2-methylpentanal and *n*BuMgCl. Using our oxidation conditions, the resulting conversion of ferrugineol, close to 70%, is satisfying. However, in the tandem process the system would be slightly different with alkylmagnesium alkoxide being produced in lieu of the

dialkoxide. Therefore, a quick survey of *n*BuMgCl as catalyst was performed, rapidly screening different solvents. It promptly appeared that a catalytic version of the reaction was not possible as the best results obtained were around 20% conversion using 0.4 equiv of *n*BuMgCl (Table 4, entry 5) and increasing this amount to 0.5 equivalents did not improve the conversion greatly. The best solvent appeared to be C_6D_6 (Table 4, entry 5) but running the reaction neat gave similar conversion (Table 4, entry 2).

Table 4. *n*BuMgCl used as catalyst of the ferrugineol/ferrugineone oxidation.



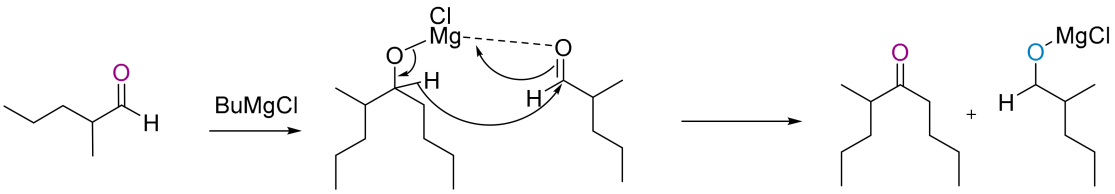
1 2

Entry	*n*BuMgCl (equiv)	Solvent	^{1}H NMR (%) Conversions [1]
entry 1	0.1 to 0.3	neat	NR
entry 2	0.4	neat	18
entry 3	0.5	neat	traces
entry 4	0.4	THF	NR
entry 5	**0.4**	**C_6D_6**	**21**
entry 6	0.4	$CDCl_3$	traces
entry 7	0.4	DME	traces
entry 8	0.4	DMF	traces

Reaction conditions: ferrugineol (1.0 equiv), aldehyde (3.0 equiv), *n*BuMgCl (0.1 to 0.5 equiv), heating 1 h at 60 °C under inert atmosphere. [1] Conversions are calculated according to the starting material consumption related to the appearance of product.

2.4.2. Proposed Synthesis of the 90/10 Mixture

Flow chemistry is allowing for a better control of the reaction conditions, thus avoiding byproducts resulting from elimination or crossed aldol reactions. It also prevents thermal runaway leading to undesired side reactions. In our systems, we would easily separate the addition of *n*BuMgCl on the aldehyde, and the subsequent oxidation of the resulting ferrugineol using the excess of aldehyde injected in the system. In that case, 2-methylpentanal would serve as both the substrate and the oxidant (Scheme 2).



Scheme 2. Tandem process of the *in situ* Oppenauer oxidation of ferrugineol.

Applying this synthesis in flow chemistry allowed us to quickly evaluate the correlation of aldehyde excess and the alcohol/ketone ratio. However, the number of equivalents of *n*BuMgCl still needed to be optimized, as well as the reaction conditions for flow application.

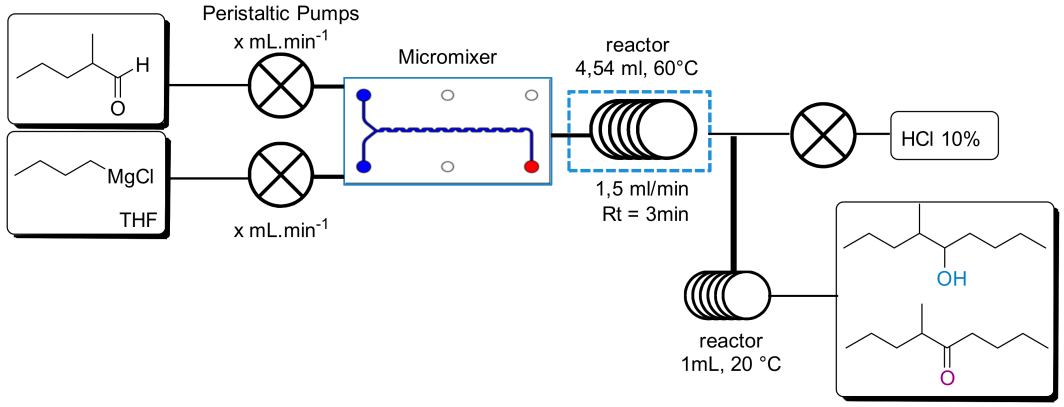
2.4.3. Optimization of Flow Conditions

A series of experiments using various temperatures or various amounts of *n*BuMgCl was performed on an E-Series of Vapourtec. As decreasing the temperature below 60 °C led to lower conversions while increasing the temperature to 70 or 80 °C did not show any evidence of improvement, we decided to process with 60 °C for the rest of the optimization.

Different amounts of *n*BuMgCl (from 0.70 to 1.10 equiv.) were tested in flow chemistry to demonstrate which conditions would be the best to get to the expected 90/10 mixture of ferrugineol/ferrugineone. The experiments were followed in GC/MS using a DB-1701 capillary column and a HP 5973 mass selective detector (EI).

Decreasing the amount from 1.10 equiv to 0.90 equiv of *n*BuMgCl led to a mixture closed to the right proportions of ferrugineol/ferrugineone (Table 5, entry 3). Finally, we found that 2-methylpentanal (1.0 equiv), *n*BuMgCl (0.90 equiv), in the absence of solvent with a 4.54 mL tubing (3 min residence time) heated to 60 °C led to the formation of the ferrugineol/ferrugineone as an 86/14 mixture in 91% yield. Over the course of 8 h of operation and with a 3 min residence time, using relatively low flow rates, 173 g of the ferrugineol/ferrugineone mixture were obtained (Figure 2).

Table 5. Optimization of flow synthesis conditions.



Entry	Aldehyde Flow (mL/min)	nBuMgCl Flow (mL/min)	nBuMgCl Conc.	nBuMgCl	% (2) (GC/MS)	% (1) (GC/MS)	Yield (%)
entry 1	0.281	1.22	2.04	1.10	0.7	99.3	60
entry 2	0.297	1.2	2.04	1.03	1.8	98.2	79
entry 3	**0.329**	**1.17**	**2.04**	**0.90**	**14.0**	**86.0**	**91**
entry 4	0.4	1.11	2.04	0.70	21.0	78.4	97

Reaction conditions: ferrugineol (1.0 equiv), aldehyde (3.0 equiv), *n*BuMgCl (0.70 to 1.10 equiv.), heating 8 h 30 at 60 °C with a residence time of 3 min. (**1**) is for ferrugineol and (**2**) is for ferrugineone.

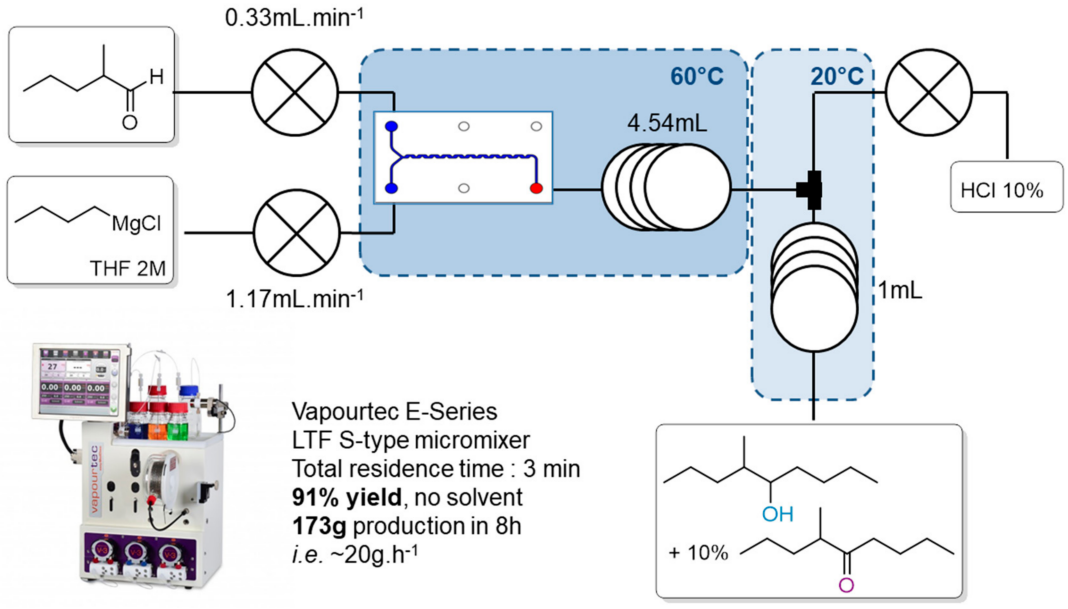


Figure 2. Flow chemistry process for the synthesis of a 90/10 ferrugineol/ferrugineone mixture.

3. Materials and Methods

All reagents and solvents were purchased from Sigma-Aldrich, (Sigma-Aldrich Chimie SARL, Tharabie France). Tribromoacetaldehyde was purchased from TCI (TCI Europe N.V., Zwijndrecht, Belgium). THF, dichloromethane, toluene and C_6D_6 were dried over sodium/benzophenone and freshly distilled under an atmosphere of argon before use. All commercially available solvents and reagents were use directly as received unless specified. All the laboratory glassware was dried in oven and cooled under vacuum before use.

Analytical thin layer chromatography (TLC) was carried out using 0.25 mm silica plates purchased from Merck. Eluted plates were visualized using aqueous $KMnO_4$ ($KMnO_4$ 3 g, K_2CO_3 20 g, aqueous 5% NaOH 5 mL, H_2O 300 mL). Silica gel chromatography was performed using 230–400 mesh silica gel purchased from Merck (Merck, Darmstadt, Germany) and more precisely from the supplier Sigma Aldrich (Sigma-Aldrich Chimie SARL, Tharabie France).

GC-MS analysis was performed with a HP 6890 series GC-system equipped with a J&W Scientific DB-1701 capillary column from Agilent (Agilent Technologies France, Les Ulis, France) and a HP 5973 mass selective detector (EI) also from Agilent (see above) using the following method: the temperature was held at 70 °C for 1 min, then the temperature increased till 230 °C with a heating rate of 20 °C/min and kept for 6 min at 230 °C.

^{1}H NMR was recorded on a 300 MHz, 400 MHz, and 600 MHz using Bruker Advance 300, Advance 400, and Advance 600, respectively (Bruker France S.A.S., Palaiseau, France). Chemical shifts (δ) are given in ppm relative to tetramethylsilane (external standard). ^{13}C NMR was recorded on a 300 MHz, 400 MHz, and 600 MHz using Brucker Advance 300, Advance 400, and Advance 600, respectively. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (external standard).

Water traces amounts were measured using a TitroLine® 7500 KF trace from Thermo Fisher Scientific (Fisher Scientific SAS, Illkirch, France) with three injections using 400µL of the solvent studied each time and the average value was reported.

A Vapourtec E-series (V-3 perilstatic pumps) flow reactor was used for flow chemistry experiments (Vapourtec Ltd., Bury St Edmunds, Suffolk, UK). The reactor consists of a 4.54 mL 1/16" PTFE tubing (0.81 mm I.D.) heated at 60 °C followed by a 1 mL 1/16" PTFE tubing (0.81 mm I.D.). The E-Series come with a touchscreen interface, mounted at an ergonomically optimal height with full tilt adjustment. It allows to easily set the key flow rates but also the temperature parameters which can be accurately controlled (± 1 °C), through a feedback system, in the range of room temperature −150 °C. (https://www.vapourtec.com/products/e-series-flow-chemistry-system-overview/).

In a typical calculation, the NMR conversion of alcohol in ketone was evaluated using the following equation and the error of measurement of the NMR is supposed to be ±5%:

$$\text{Conversion } \% = \frac{\frac{I\text{ketone}}{\text{number of protons considered}}}{\frac{I\text{ketone}+I\text{alcohol}}{\text{number of protons considered}}} \times 100$$

where I is the integral value of protons from alcohol and ketone in the spectrum of reaction mixture.

4. Conclusions

Overall, we developed an efficient and selective method for the oxidation of various alcohols to the corresponding aldehydes and ketones under mild conditions. This unprecedented Mg-catalyzed OPP oxidation highlights the efficiency and importance of the OPP method for the oxidation of primary and secondary alcohols and in the same time illustrates interesting versatile reactivity of magnesium derivatives. This protocol has notable advantages as it mostly uses common and inexpensive chemicals, operates with short reaction times especially using flow systems, gives good yields, lack of usual byproducts and can be applied to the oxidation of many alcohols. In addition, studying the reactivity of Grignard's reagents associated with the main advantages of continuous flow chemistry led to the

development of a new procedure to selectively synthesize more than 170 g of a natural pheromone mixture with a perfect control of the ratio owing to the flexibility of the system.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/8/11/529/s1, Figure S1: ^{1}H NMR of pure Ferrugineol (**1**), Figure S2: ^{1}H NMR of pure Ferrugineone (**2**), Figure S3: ^{1}H NMR of Table 1 Entry 1. $MgCl_2$ (0.4 equiv), 100 °C, 3 h, Figure S4: ^{1}H NMR of Table 1 Entry 2. $Mg(OH)_2$ (0.4 equiv), 100 °C, 3 h, Figure S5: ^{1}H NMR of Table 1 Entry 3. $Mg(OEt)_2$ (0.4 equiv), 100 °C, 3 h, Figure S6: ^{1}H NMR of Table 1 Entry 4. $Mg(OEt)_2$ (0.4 equiv), 100 °C, 6 h, Figure S7: ^{1}H NMR of Table 1 Entry 5. MgO (0.4 equiv), 100 °C, 3 h, Figure S8: ^{1}H NMR of Table 1 Entry 6. $Mg(O\mathit{t}Bu)_2$ (0.3 equiv), 110 °C, 1 h, Figure S9: ^{1}H NMR of Table 1 Entry 6—Zoom from 5ppm to 0ppm—Protons attribution, Figure S10: ^{1}H NMR of Table 1 Entry 7. $Mg(O\mathit{t}Bu)_2$ (0.3 equiv), 60 °C, 1 h, Figure S11: ^{1}H NMR of Table 1 Entry 8. $Mg(O\mathit{t}Bu)_2$ (0.3 equiv), 60 °C, 3 h, Figure S12: ^{1}H NMR of (**4j**). $Mg(O\mathit{t}Bu)_2$ (0.3 equiv), 60 °C, 1 h, Figure S13: ^{1}H NMR of (**4l**). $Mg(O\mathit{t}Bu)_2$ (0.3 equiv), 60 °C, 1 h.

Author Contributions: M.P.: idea, structure, and design of the paper; planning for the work related to the publication; supervised analyzes of data; M.P. is the main supervisor. V.L. did the batch experiments and flow experiments, optimized most of the reaction conditions and analyzed the data. M.B. wrote the manuscript, is the supervisor of the bachelor student C.B., analyzed the data of C.B. C.B. performed the last optimization experiments and isolated products under the supervision of M.B. All authors have read, critically reviewed, and agreed to the final version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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