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COMMUNICATIONS

Sequential α-lithiation and aerobic oxidation of an arylacetic acid - continuous-flow synthesis of cyclopentyl mandelic acid

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Abstract

The development of a multistep continuous-flow process, consisting of a direct α-lithiation stage and subsequent hydroxylation by aerobic oxidation, is reported. The protocol is applied to the synthesis of cyclopentylmandelic acid (CPMA), the main building block for the anticholinergic glycopyrronium bromide (glycopyrrolate). We demonstrate the safe utilization of organolithium reagents and molecular oxygen in combination by using a continuous-flow protocol. The first stage involves the formation of a di-lithium enolate intermediate, which was either pre-formed in batch or formed in flow by using *n*-hexyllithium as a cost-effective and industrially safe base. The subsequent hydroxylation stage utilized molecular oxygen under homogeneous and mild conditions (atmospheric pressure and room temperature) to give the desired product. A diluted form of oxygen gas, consisting of less than 10% O_2 in N_2 ("synthetic air"), is used in pharmaceutical batch manufacturing to effectively address safety concerns when handling molecular oxygen. The telescoped flow process afforded the target intermediate in 65% solution NMR yield (50% isolated yield after re-crystallization). The continuous-flow process opens up new opportunities for the manufacture of CPMA, with a protocol which can safely handle pure O_2, and compares favorably with existing Grignard-based batch processes.

Keywords Glycopyrrolate (glycopyrronium bromide) · Cyclopentyl mandelic acid (CPMA) · Continuous-flow · Gas-liquid transformations · Molecular oxygen · Organometallics

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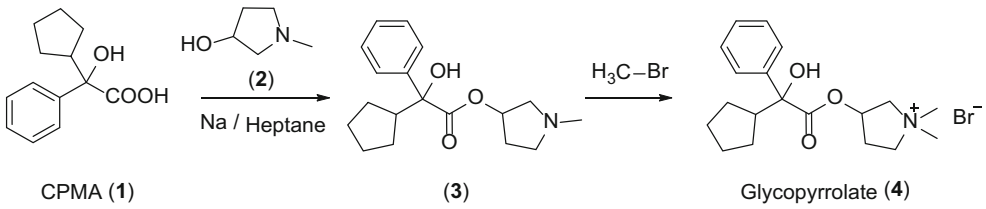
The medicinal properties of glycopyrronium bromide (glycopyrrolate, **4**) were first identified in the late 1950s [1]. G*lycopyrrolate* is an antagonist of muscarinic cholinergic receptors and is used for the treatment of drooling or excessive salivation (sialorrhea) [2], excess sweating (hyperhidrosis) [3], and overactive bladder and for presurgery treatment. In addition, it has recently been introduced as an effective bronchodilator for the treatment of chronic obstructive pulmonary disease (COPD) for asthma patients [4]. Glycopyrrolate displays few side effects because it does not pass through the blood brain barrier. Cyclopentyl mandelic acid (CPMA, **1**), or its corresponding ester derivatives, are key intermediates in the synthetic routes to **4**. CPMA (**1**) reacts with 1-methylpyrrolidin-3-ol (**2**) to form tertiary amine **3**. *N*-Methylation of **3** by methyl bromide gives quaternary ammonium salt glycopyrrolate **4** as a racemate (Scheme 1) [5].

CPMA (**1**) is a synthetically challenging intermediate to prepare (Scheme 2). Routes A to D are most likely to be the commercially applied methods because these procedures are

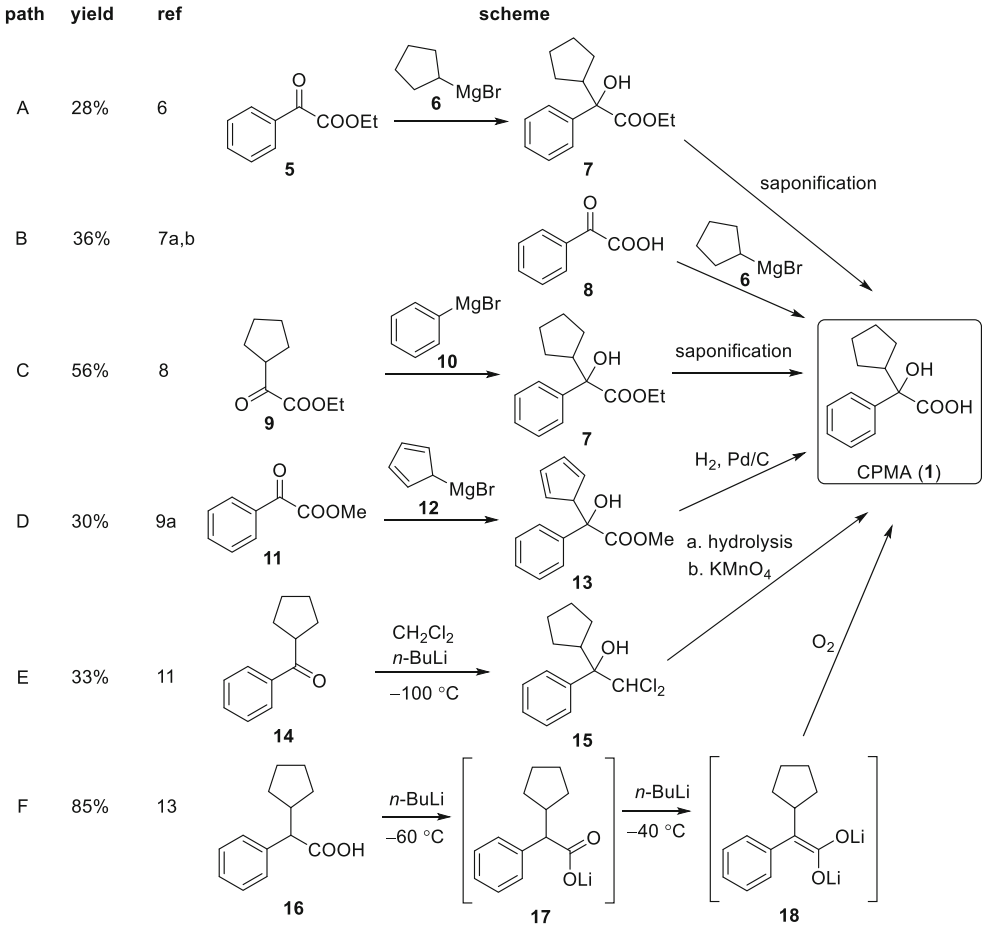
Scheme 1 Synthesis of glycopyrrolate **4** from CPMA (**1**)



described in patents [5]. The published descriptions for the yields of **1** range from 28 to 56% for routes A to D. Ethyl phenylglyoxylate is reacted with cyclopentyl magnesium bromide to form an ester which is then hydrolyzed (route A) [6]. Phenylglyoxylic acid can be reacted in a similar manner with cyclopentyl magnesium bromide to directly form **1** (route B) [7]. Alternatively, the inverse addition of phenyl-Grignard reagent to cyclopentyl glyoxylic acid ester is reported (route C) [8]. Cyclopentyl glyoxylic acid ester can also be reacted with cyclopentadienyl magnesium bromide which is followed by an additional hydrogenation step with Pd/C and H_2 to afford **1** (route D) [9, 10].

There are two further methods that are less likely to be used at industrial scales due to safety concerns and the very low reaction temperatures employed (routes E and F). Dichloromethane is deprotonated by *n*-butyllithium (*n*-BuLi) at −100 °C and reacted with phenyl-cyclopentyl ketone, which is subsequently hydrolyzed and oxidized with potassium permanganate to give **1** (route E) [11]. The highest yielding reported protocol utilizes molecular oxygen for the hydroxylation of cyclopentyl phenyl acetic acid (route F). Adam and Cueto described the formation of lithium carboxylate **17** at −60 °C by an equivalent of *n*-BuLi, and after 60 min the second equivalent of *n*-BuLi formed the di-lithium enolate **18** at −40 °C. Oxygen was then bubbled through the α-lithiocarboxylate solution at room temperature [12]. CPMA (**1**) was prepared by the procedure described by Adam and Cueto in a remarkable 85% isolated yield [13]. However, the authors noted that "*the system was very sensitive to reaction conditions and required particular attention, in the presence of excess n-BuLi (equivalent ratio 0.9:1), to the exposure of the base and to the bubbling oxygen.*" The inverse addition of

Scheme 2 Existing synthetic pathways to CPMA (**1**)



di-lithiated carboxylic acid to a solution with bubbling oxygen at low temperature (−78 °C) afforded the α-hydroperoxy acids [12]. Moersch and Zwiesler were the first to report a procedure for the synthesis of α-hydroxycarboxylic acids from their corresponding carboxylic acids by using air as the oxygen source [14]. Air was bubbled through a solution of the di-lithiated carboxylic acid at room temperature over a prolonged time (18 h) to prepare the α-hydroxycarboxylic acids in low to moderate yields.

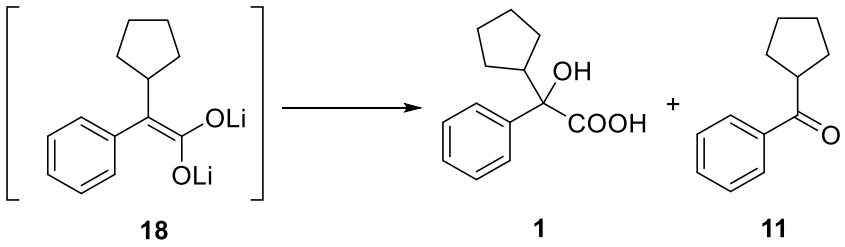
Molecular oxygen is highly abundant, environmentally benign, inexpensive and easy to separate from product mixtures. However, it is underutilized in organic synthesis due to safety concerns, particularly at large scales [15]. Historically, the pharmaceutical industry has used batch processes for the manufacture of active pharmaceutical ingredients (APIs). Within a batch reactor, high concentrations of oxygen/organic vapor would exist within the headspace when using O_2 gas, which is a large inventory of a potentially flammable mixture. A common strategy applied in pharmaceutical manufacturing is to operate below the limiting oxygen concentration (LOC) value by using a diluted form of oxygen gas, consisting of less than 10% O_2 in N_2 ("synthetic air") [16]. The LOC value is defined as "the minimum partial pressure of oxygen that supports a combustible mixture". Operating below the LOC value ensures the oxygen/organic vapor never enters the explosive regime. However, there can be limitations in terms of process efficiency, including reaction rate and product selectivity, in using diluted air in comparison to pure air. Alternatively, the recent transition from batch to continuous processing in pharmaceutical manufacturing has enabled the safe handling of hazardous chemistry [17], including the ability to handle liquid-phase aerobic oxidations, even at large scales [18]. The precise temperature control and the small channel dimensions of continuous-flow reactors provide a high surface-to-volume ratio enabling the generated heat to be dissipated quickly. With sufficient understanding of a reaction system and adequate process design to address safety concerns and mitigate risks, aerobic oxidations utilizing pure molecular oxygen can be adopted at large scales through the utilization of appropriate continuous-flow processing systems [18]. In addition, pioneering work by Yoshida and others have demonstrated organometallic reagents can be handled at higher temperatures than the standard cryogenic conditions applied under batch conditions when using continuous-flow reactors [19]. Based on the success reported by our group and others for liquid-phase oxidations using continuous-flow reactors, we were encouraged to explore the development of a continuous-flow process for route E as a safe and cost-effective alternative to the existing synthesis strategies. We herein report the development of a multistep continuous-flow protocol for CPMA (**1**) synthesis via the hydroxylation of cyclopentylphenylglycolic acid by using organolithium reagents and molecular oxygen.

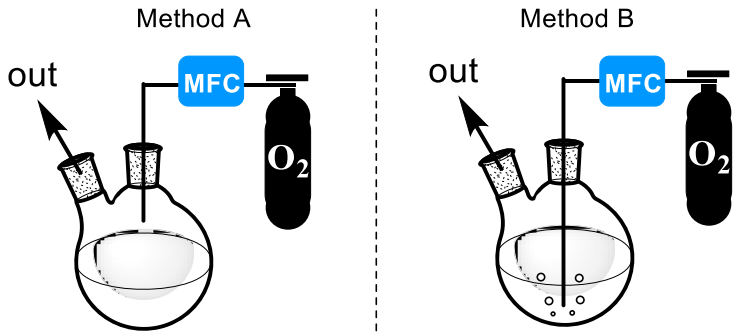
We commenced our studies by examining the critical parameters in batch experiments. The di-lithium enolate **18** formation by reaction of cyclopentylphenylglycolic acid (**16**) with *n*-BuLi, and the subsequent hydroxylation of the di-lithium enolate by using O_2 were studied separately. α-Phenylcyclopentylacetic acid (**16**) was reacted with *n*-BuLi and then trapped by deuterium oxide (D_2O) with the optimal base equivalents and temperature evaluated (Table S1). D_2O is a liquid at room temperature and therefore was easier to handle than O_2 gas for preliminary studies. Conditions were sought that kept the lithium species in solution to ensure the reaction was amenable to flow processing. The lithium carboxylate intermediate **17** was identified to be particularly prone to precipitation when using THF/hexanes in 50/50 ratio. The monolithium intermediate precipitation was avoided by adding the *n*-BuLi as a single portion, rather than as two separate portions, and by using a solvent composition ratio of THF/hexanes ≥77/23. The batch experiments showed that the di-lithium enolate was successfully formed after trapping with D_2O in 87% yield with 3 equivalents of *n*-BuLi at 25 °C and a reaction time of 5 min.

The hydroxylation stage by using molecular oxygen was examined by using a pre-formed solution of the di-lithium enolate **18** (see above). The concentration of the di-lithium enolate solution assumed 100% conversion of starting material. The O_2 was introduced into the batch reactor in a controlled manner by using a mass flow controller (MFC, EL-Bronkhorst). A stream of O_2 (5 mL_n min^{-1} or 25 mL_n min^{-1}) was introduced to a 10 mL round bottom flask containing di-lithium enolate solution (0.25 M, 2 mL). The O_2 was introduced into the flask through a needle, either: (i) above the liquid-phase (Method A); or (ii) bubbled through the di-lithium enolate solution (Method B). The conversion of **18** was slower when the O_2 was introduced above the liquid-phase (entries 1 and 2) due to a lower concentration of O_2 dissolved in solution. In this scenario the reaction rate is controlled by the mass transfer of oxygen into the liquid phase. When the O_2 was bubbled through the solution the conversion of **18** was complete after 3 min (entry 3) and no CPMA (**1**) decomposition was observed over time (entry 4). The batch experiments indicated that a higher excess of oxygen (entry 5) or lower temperatures (entry 6) favored the formation of undesired byproduct **11**. The formation of **11** is proposed to occur through oxidative decarboxylation of α-hydroperoxides, formed from the di-lithium enolate, by molecular oxygen [21]. (Table 1).

The next stage was to assemble a flow reactor for the lithiation step. The di-lithium enolate formation was again first conducted by using *n*-BuLi as base and through trapping by D_2O to optimize for residence time and reactor type. Two different flow reactor configurations were investigated: a glass microchip (Syrris, 1 mL internal volume) and a PTFE tubular coil (varying volumes, 0.8 mm internal diameter). The two

Table 1 Preliminary batch investigation of hydroxylation by using molecular oxygen[a]





Entry	Method	O_2 flow rate [mL_n min^{-1}]	T [°C]	Reaction time [min]	**18** conv. [%][b]	**1** yield [%][b]	**11** yield [%][b]
1	A	5	25	3	79	64	trace
2	A	5	25	120	96	60	2
3	B	5	25	3	100	65	trace
4	B	5	25	120	100	65	trace
5	B	25	25	3	100	48	10
6	B	5	−40	3	100	13	48

[a] Conditions: pre-formed di-lithium enolate solution prepared by using 16 (0.25 M in THF/hexane 77/33), n-BuLi (3 equiv.), rt., 5 min, under Ar atmosphere. Hydroxylation conditions: 750 rpm, 1 bar

[b] The reactions were quenched with MeOH followed by acidification with H_3PO_4 in an ice bath. Conversion and yields were measured by ^{1}H NMR using mesitylene as an internal standard

feeds were introduced using two syringe pumps (Syrdos) and either mixed within the microchip or with a T-piece in the case of the PTFE reactor. A sample injection loop (SL) was utilized for the *n*-BuLi feed, ensuring that the organolithium reagent was not introduced directly through the pump and therefore minimizing corrosion of the wetted parts. The microchip and coil were submerged within an ultrasound bath to prevent lithium salt precipitation which could block the reactor channels. Unfortunately, the product yields were lower than for the batch experiments (Table S2). The flow experiments demonstrated that the starting material was converted in less than 5 min residence time (Fig. 1). Subsequently, a base screen was conducted (Table S3). LDA and LHMDS resulted in no conversion of **16**, probably because these bases are too hindered to deprotonate the benzylic position. In addition to *n*-BuLi, *n*-hexyllithium (HexLi) reagent emerged as the most suitable, efficient, cost-effective and industrially safe base. The limitation of using *n*-BuLi is the evolution of flammable butane gas as a byproduct, which becomes more difficult to handle at larger scales [22]. Slightly higher conversion was achieved by using a glass microchip (Fig. 1), however clogging by lithium salts frequently occurred within the

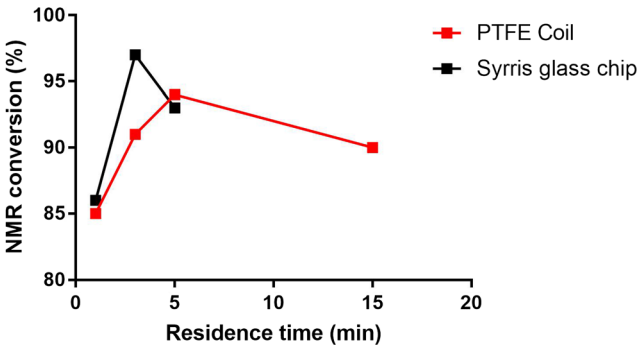
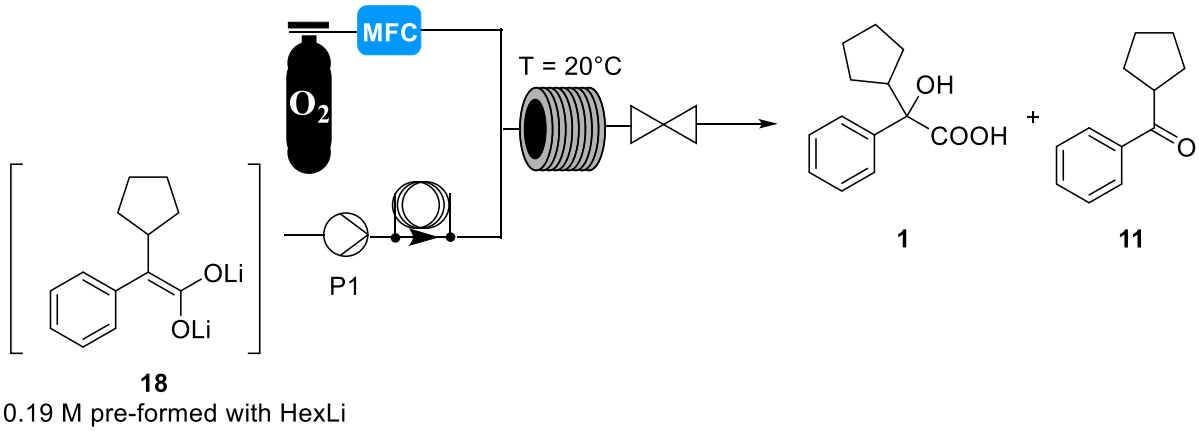


Fig. 1 Compound **16** conversion (%) versus residence time when using *n*-BuLi as base in two different flow reactors: (red curve) PTFE coil reactor, (black curve) Syrris glass chip

microchip, thus the PTFE reactor was favored for future experiments to provide better scalability. HexLi is the base used in the subsequent experiments described in this manuscript, further optimization studies on the lithiation step using HexLi as base are reported in Table S4.

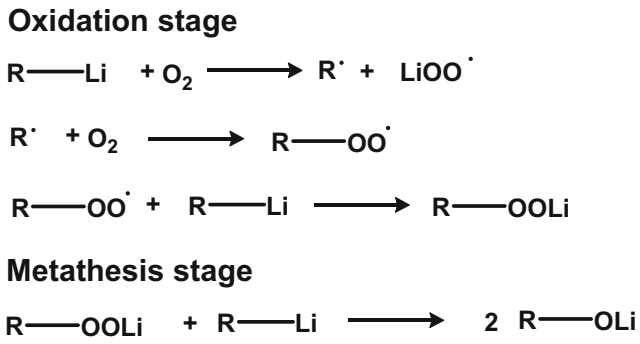
Extending our investigation to HexLi, we prepared the pre-formed enolate for trials with molecular oxygen in flow [23]. We investigated the influence of residence time, pressure and temperature on the reaction outcome. For the hydroxylation, the pre-formed lithium enolate solution was loaded through a sample loop (SL) and pumped into the system using a syringe pump (Syrdos) [23]. The pre-formed di-lithium enolate in THF solution was stable for 3 h at room temperature. The oxygen was introduced by using a mass flow controller (MFC) calibrated for oxygen. The initial flow experiments were conducted within a microchip (Syrris, 1 mL) with residence times in the order of seconds. The system pressure was maintained using a back pressure regulator (BPR, Zaiput) at either 1 or 4 bar. The reaction produced a biphasic, segmented flow regime above 1 equivalent of oxygen. The high interfacial area generated in flow significantly accelerates the dissolution of O_2 into the liquid phase. Under these conditions, complete conversion of starting material was observed, but poor product selectivity was obtained. The negative influence of excess oxygen on our desired reaction encouraged us to test at atmospheric pressure within the flow system and at lower equivalents of oxygen which would reduce the concentration of oxygen dissolved in solution. The oxygen was completely soluble giving homogenous solutions below 1 equivalent of oxygen. Full starting material conversion and 60% product yield were achieved by decreasing to 0.4 equivalents of oxygen at a 10 min residence time (Table 2, Entry 6). The reaction was very sensitive to small changes in the operating conditions. The high flow rates resulted in very good gas-liquid

Table 2 Continuous-flow optimization for hydroxylation step using a pre-formed enolate with HexLi[a]



Entry	O_2 equiv.	T [°C]	Reactor volume [mL]	t_{res} [min]	**18** conv. [%][a]	**1** yield [%][a]	**11** yield [%][a]	**1**:**11** select.
1	0.5	25	11	51	>99	41	4	91:9
2	0.5	25	3	10	99	50	6	90:10
3	0.5	0	3	10	99	28	6	82:18
4	0.5	25	3	7	97	76	11	93:7
5	0.5	25	3.4	3	51	37	3	97:3
6	0.4	25	3	10	96	60	2	97:3
7	0.4	25	5	15	97	61	2	97:3
8	0.3	25	6	15	80	40	1	97:3
9	1.0	25	3	0.57	99	15	14	73:27
10	1.0	0	3.4	0.57	>99	26	70	27:73

[a] Conditions: **18** (0.19 M in THF/hexanes 77:33), rt., 5 min, under Ar atmosphere. 750 rpm, 1 bar. Flow setup: A syringe pump (Syrdos) was used to pump the liquid feed, the di-lithium enolate solution was introduced using a sample loop, a mass flow controller (MFC, EL-Bronkhorst) introduced O_2 gas, the feeds either mixed with a Y-piece before entering a PTFE coil reactor, and a back pressure regulator (BPR, Zaiput) maintained a constant system pressure. See Table S6 for liquid pump and O_2 flow rates and PTFE reactor volumes. The reactions were quenched with MeOH followed by acidification with H_3PO_4 in ice. Conversion and yield are measured by ^{1}H NMR using mesitylene as an internal standard

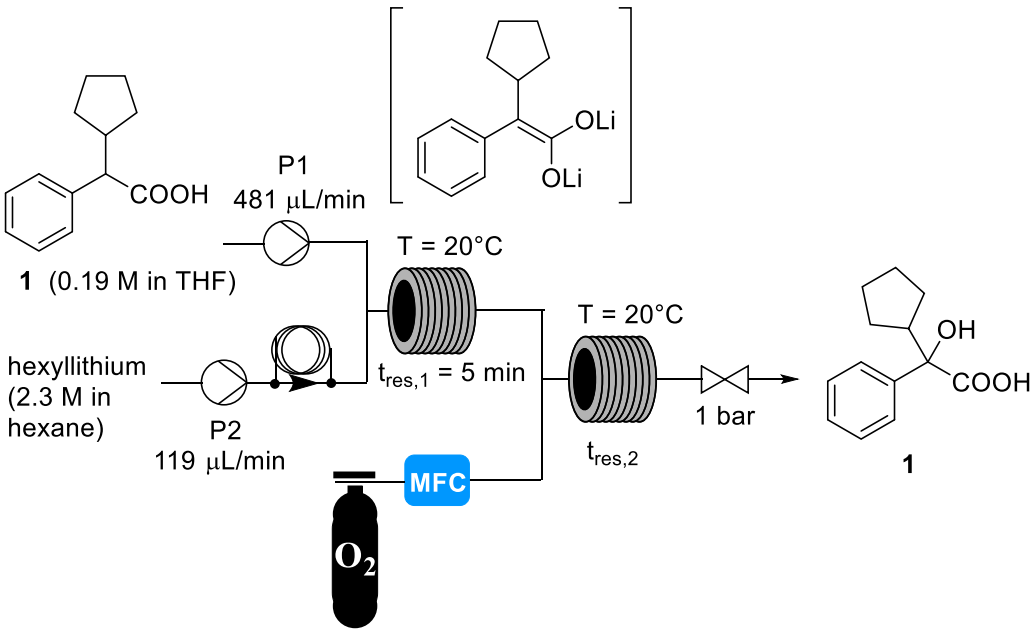


Scheme 3 Postulated reaction mechanism

mixing improving the availability of the oxygen in solution and promoting the formation of ketone **11** as by-product, whereas employing lower equivalents of oxygen resulted in a system that was starved of oxygen and promoted better desired product selectivity. Gratifyingly, by using 0.5 equivalent of oxygen and 7 min of residence time we obtained 76% yield desired product despite forming the ketone in 11% yield (Table 2, entry 4). The ketone could easily be removed from the crude product with an acid-base work-up protocol. These experiments were compared to pre-forming the enolate with *n*-BuLi (Table S5), which required longer residence times. Interestingly, the requirement of sub-stoichiometric oxygen gives an indication on the reaction mechanism (Scheme 3). It is likely that molecular oxygen promotes an initial formation of a benzylic radical subsequently evolving into a peroxy radical. Then the lithium peroxy compound undergoes metathesis with a lithium enolate molecule to form two hydroxylated products [20].

Finally, the individual α-lithiation and aerobic oxidation steps were incorporated into a multi-step continuous-flow set-up (Table 3). Direct translation of the optimal conditions from the single steps resulted in 57% conversion and 44% yield.

Table 3 Continuous-flow optimization for sequential α-lithiation using HxLi and aerobic oxidation



Entry	O_2 equiv.	$t_{res,2}$ [min]	**16** conv. [%][b]	**1** yield [%][b]	**11** yield [%][b]
1	0.5	10	57	44	trace
2	0.6	7	84	44	trace
3	0.6	10	86	56	trace
4[c]	0.6	18	90	65	trace
5	0.6	28	92	58	trace
6	0.7	7	92	52	trace
7	0.8	7	92	53	10
8	0	7	0	0	0

[a] Conditions: **16** (0.19 M in THF), hexyllithium (2.3 M in hexane). The reactions were quenched with MeOH followed by acidification with H_3PO_4 in ice. Conversion and yield are measured by ^{1}H NMR using mesitylene as an internal standard. [c] Procedure for entry 4 is described in the experimental section

Slight modifications were necessary to the conditions for the aerobic oxidation step, thus illustrating the sensitivity of the reaction outcome to the reaction conditions. The optimal conditions were identified as 0.6 equivalents of O_2 and 18 min of residence time to give 90% conversion and 65% yield (Table 3, entry 4). Longer residence times and using ≥0.7 equivalents of O_2 were detrimental to yield, even if higher conversion was obtained (Table 3, entries 5 to 7). After re-crystallization, pure CPMA (**1**) was isolated in 50% yield.

In conclusion, a continuous-flow protocol was developed for the synthesis of cyclopentylmandelic acid (CPMA, **1**), an important intermediate in the synthesis of glycopyrronium bromide (glycopyrrolate). The two reaction steps were investigated separately in batch and in flow to identify the critical parameters. The system was very sensitive to changes in the reaction conditions and equipment configuration. The process was developed to utilize *n*-hexyllithium as an industrially suitable base. O_2 gas could be dosed continuously in a safe and accurate manner using a mass-flow controller for the aerobic oxidation step. It was identified that low equivalents of O_2, atmospheric pressure and room temperature favored the desired product. On the other hand, high concentrations of oxygen, high pressure and low temperatures favored the undesired oxidative decarboxylation pathway to form a ketone side product. The lithiation reaction proceeded with 5 min residence time and the aerobic oxidation with 18 min residence time to give the target compound in 65% solution NMR yield (50% isolated yield after re-crystallization) under the optimal reaction conditions [23]. This yield is superior to the yields obtained applying traditional Grignard-based protocols (Scheme 2).

Representative procedure for the preparation of CPMA [1] using continuous-flow conditions (Table 3, entry 4) Flow experiments were performed using the continuous-flow setup depicted in Table 3. A 2.3 M solution of *n*-hexyllithium in hexane was introduced through a sample loop. The liquid feed containing *n*-hexyllithium in hexane was pumped using a syringe pump (Syrdos) with a flow rate of 119 μL/min, using THF as a carrier solvent. A 0.19 M solution of α-phenylcyclopentylacetic acid (**16**) in THF (anhydrous) was pumped directly through the second syringe pump (Syrdos) with a flow rate of 481 μL/min. The two streams were mixed using a T-piece into a tubular reactor (3 mL, 0.8 mm internal diameter, PTFE coil) to provide 5 min residence time. The T-piece and reactor were submerged within an ultrasound bath at 25 °C to avoid lithium salt precipitation within the channel. On formation of the di-lithium enolate within the solution an intense dark red color was observed. The third feed consisted of O_2 gas and was dosed at a flow rate of 1.28 mL_n/min with a calibrated mass flow controller (EL-Flow, Bronkhorst). The gas flow rate was measured in units of mL_n/min (n represents measurement under standard conditions: $T_n = 0$ °C, $P_n =$ 1.01 bar). The enolate solution and molecular oxygen were mixed using a Y-mixer into a tubular reactor (11 mL, 0.8 mm internal diameter, PTFE coil) at room temperature to give a homogeneous solution and providing 18 min residence time. The pressure was maintained at 1 bar by using a back pressure regulator (Zaiput). The output material was collected for one residence time worth of material (23 min) within a round bottom flask containing MeOH (4 mL) under N2. The solution obtained was then evaporated under reduced pressure. Crystallization was achieved with hexane/chloroform (9:1). The chloroform was removed under reduced pressure which resulted in product precipitation. Subsequent filtration afforded pure CPMA (**1**) (230 mg, 1.05 mmol, 50% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.68 (2H, d, *J* 8.1 Hz), 7.42–7.3 (3H, m), 2.95 (1H, q, *J* 8.2 Hz), 1.76–1.28 (8H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 180.64, 141.13, 128.36, 127.90, 126.02, 79.30, 47.32, 27.08, 26.56, 26.44, 26.03.

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