Continuous Flow Synthesis of Ketones from Carbon Dioxide and Organolithium or Grignard Reagents**

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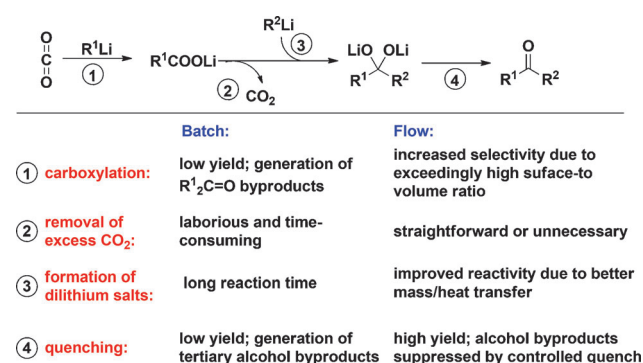
Abstract: *We describe an efficient continuous flow synthesis of ketones from CO_2 and organolithium or Grignard reagents that exhibits significant advantages over conventional batch conditions in suppressing undesired symmetric ketone and tertiary alcohol byproducts. We observed an unprecedented solvent-dependence of the organolithium reactivity, the key factor in governing selectivity during the flow process. A facile, telescoped three-step–one-flow process for the preparation of ketones in a modular fashion through the in-line generation of organometallic reagents is also established.*

Ketones are fundamental structural motifs in the synthesis of pharmaceuticals, natural products, functional materials, and agrochemicals.[1] As such, the efficient preparation of ketones is of great significance to chemical, medicinal, and material science. The most common methods of synthesizing ketones are Friedel–Crafts acylation and oxidation of secondary alcohols. Reactions of carboxylic acid derivatives, such as nitriles, Weinreb amides, anhydrides, and acid chlorides with metallic reagents have also emerged as important alternatives for the synthesis of the corresponding ketones.[2] In this context, the direct conversion of a carboxylic acid into a ketone by using at least two equivalents of an organolithium reagent has long been studied and is still receiving significant attention.[3] An even more straightforward and convenient strategy was reported by the Breitmaier group: the one-pot synthesis of ketones from two organolithium reagents and carbon dioxide.[4]

Herein, we report the development of an efficient process to synthesize ketones from organolithium reagents and CO_2 in continuous flow systems. Through this approach, a wide range of substituted ketones can be easily obtained and the formation of symmetric ketone or tertiary alcohol byproducts is almost completely suppressed. An important and unprecedented trend pertaining to the reactivity of organolithium

reagents based on solvent selection was also observed in this study. Notably, the stoichiometry of CO_2 gas (1 equiv or 2.5 equiv, depending on the reactivity of the organolithium reagent) can be easily controlled by a mass flow controller (MFC) in the continuous system. Moreover, Grignard reagents are also well-suited to our flow system, and are complementary to the lithium reagents in that they broaden the substrate scope of these reactions, which represents the first example of the direct synthesis of ketones through a Grignard/CO_2/organolithium sequence. In addition, a facile, modular, telescoped three-step–one-flow preparation of ketones has been realized through the incorporation of the in-line generation of functionalized organolithium or organo-magnesium species.

The reported one-pot batch process involves four steps (Scheme 1): 1) carboxylation of organolithium R^1Li with CO_2; 2) removal of excess CO_2; 3) introduction of R^2Li to

		Batch:	Flow:
①	**carboxylation:**	low yield; generation of $R^1_2C=O$ byproducts	increased selectivity due to exceedingly high suface-to volume ratio
②	**removal of excess CO_2:**	laborious and time-consuming	straightforward or unnecessary
③	**formation of dilithium salts:**	long reaction time	improved reactivity due to better mass/heat transfer
④	**quenching:**	low yield; generation of tertiary alcohol byproducts	high yield; alcohol byproducts suppressed by controlled quench

Scheme 1. Ketone synthesis from CO_2 and organolithium reagents.

afford a dilithium intermediate, which is believed to be stable during the reaction process,[3c] and 4) quenching to accomplish the ketone product. This method is attractive since ketones with almost any substitution pattern can be accessed directly by the selection of the two organolithium compounds. Another intriguing characteristic of this reaction scheme is the utilization of CO_2 as a renewable, nonflammable, non-toxic, and cheap C_1 feedstock, which satisfies the criteria of "green" chemistry.[5] However, these reported batch conditions suffer from several drawbacks. Firstly, carboxylation of organolithium reagents with CO_2 is frequently accompanied by the generation of symmetric ketone byproducts. High concentrations of CO_2 (achieved by the slow addition of organolithium reagents to solid dry ice) and low temperatures are thus required.[6] Secondly, the necessary removal of excess CO_2 compromises utility and throughput, particularly on large scale.[4] Thirdly, a long reaction time is generally needed

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for complete consumption of the intermediate carboxylic lithium salt.[3c] Additionally, a troublesome side reaction is the simultaneous formation of tertiary alcohols due to the relatively slow hydrolysis of unreacted organolithium reagents.[3,4]

Continuous flow synthesis has opened up new strategies and tactics for synthetic organic chemistry.[7,8] Given that continuous flow systems are generally more efficient than conventional batch conditions for biphasic gas/liquid reactions,[8,9] we envisioned that the flow synthesis of ketones would be a means to overcome all the drawbacks associated with the analogous batch synthesis (Scheme 1): 1) The exceptionally high interfacial contact between gas and liquid phases should enhance the selectivity and reactivity of carboxylation. 2) The excess CO_2, which has negative effects on the downstream reaction, can be easily removed by integration of a mini-vacuum degasser. This step may even be avoidable by using stoichiometric amounts of CO_2, which is generally challenging in batch reaction. 3) Enhanced mass and heat transfer may increase the rate of dilithium intermediate formation. 4) The dropwise addition of the final reaction mixture into quenching reagents should help to prevent the formation of tertiary alcohol byproducts.[10]

We initially tested the reaction of (trifluoromethyl)phenyllithium with CO_2 in the flow system to allow rapid optimization of carboxylation conditions.[11] Due to the instability of organolithium reagents, peristaltic pumps or Asia pumps were used and the lithium species were stored at low temperature (0 °C or −20 °C) during the flow process.[12] A low concentrated organolithium–THF solution (0.1 M) was used to preclude blocking of the reactor by precipitation of lithium salts. CO_2 gas was metered into the system through an MFC,[13] mixed with the lithium solution in a polyetheretherketone (PEEK) Y-mixer, and reacted downstream in a perfluoroalkoxyalkane (PFA) tubing reactor coil (0.4 mL, inner diameter (ID) 0.04″). As shown in Table 1, the flow system led to improvements in the selectivity for acid product **2** (entries 4 and 5 versus entries 1–3). Even at ambient temperature with one equiv CO_2, the acid was formed in 19% yield after quenching with a 1 M HCl solution (entry 4). Gratifyingly, with a simple solvent change from Et_2O to THF, the symmetric

ketone **3** was almost completely suppressed when only a stoichiometric amount of CO_2 was used (entry 6). It is notable that the observed lower reactivity of the organolithium compound in THF compared to Et_2O was unexpected based on literature reports that the reaction of organolithium reagents with 1,1-diphenylethylene was found to be substantially slower in Et_2O than in THF.[14]

Carboxylation of a variety of organolithium reagents has been examined using stoichiometric CO_2 in the flow system; the results are summarized in the Supporting Information. Depending on the reactivity of organolithium reagents towards CO_2, two complementary flow systems (**A** and **B**) were developed to achieve ketone products (Table 2). Continuous-flow system **A** was suited for reactions using stoichiometric amounts of CO_2 and consisted of two pumps, an MFC, two reactors made of PFA tubing, and a quenching bath with strong magnetic stirring. If excess (approximately 2.5 equiv) CO_2 was used to prevent symmetric ketone byproduct formation in the carboxylation step, a mini

Table 1: Optimization of organolithium carboxylation.

Entry	System	CO_2	T [°C]	Yield of **2** [%]	Yield of **3** [%]	Yield of **4** [%]
1[a]	batch	massive dry ice	0	64	30	6
2[a]	batch	bubbled gas	0	0	89	11
3[a]	batch	bubbled gas	−78	43	50	7
4[b]	flow	ca. 1 equiv	rt	19	70	10
5[b]	flow	ca. 3 equiv	rt	66	33	0
6[b,c]	flow	ca. 1 equiv	rt	96	4	0

[a] Data from Ref. [6b]. [b] Reaction conducted in 0.1 M Et_2O. Yield based on the crude ^1H NMR spectrum with trichloroethylene as the external standard. [c] Utilizing THF as the solvent.

Table 2: Complementary flow systems for ketone synthesis from organolithiums and CO_2.[a]

[a] Yield of the isolated product. [b] 1.15 Equiv of CO_2 was used. [c] The yield was calculated from the crude ^1H NMR spectrum of the unpurified product mixture with trichloroethylene as the external standard. Productivity: (0.04 mmol min^{-1}) × yield [%]. [d] Yield of the isolated product based on 5 h continuous collection of products.

vacuum degassing chamber (670 µL) was integrated into the flow system before the addition of the second organolithium reagent (Table 2, system **B**). Back-pressure regulation was not needed since all reactions were conducted under ambient pressure.

PhLi (as R^1Li) and nBuLi (as R^2Li) were used initially to optimize the solvent selection, flow rate, and quenching method under continuous flow conditions.[15] THF was selected as the solvent for R^1Li to avoid symmetric ketone byproducts, and Et_2O was used as the solvent for R^2Li to increase the reaction rate. It was gratifying that full conversion of the carboxylithium intermediate could be achieved at room temperature within 10 min. The optimized experimental procedure is summarized as follows: a peristaltic pump was used to feed the PhLi–THF solution (0.1 M, stored at 0°C) at 400 µL min^{-1}, while the CO_2 stream (ca. 2.5 sccm, ca. 3 equiv) was metered into the system using an MFC. The gas and liquid streams met at a Y-mixer, and the reaction occurred at room temperature in the PFA sample loop (0.4 mL, ID 0.04″). Next, excess CO_2 gas was separated from the slug-flow regime through a mini vacuum degasser (containing a thin porous membrane that selectively released the gas under vacuum). The organic solution was then mixed with the nBuLi–Et_2O solution (0.3 M, stored at rt, 200 µL min^{-1} flow rate) in a T-mixer and reacted in the second PFA sample loop (6 mL, ID 0.062″). Finally, the product stream was dripped into a strongly stirred 1 M HCl or NH_4Cl aqueous solution kept at 0°C. If carboxylation was achieved in high selectivity with stoichiometric CO_2 (ca. 0.9 sccm), the vacuum degasser was not needed.

With the optimal conditions established, we examined the generality of the flow synthesis of ketones using organolithium reagents with a range of substitution patterns (Table 2). Compared to the long reaction times required under batch conditions, all flow reactions were accomplished at ambient temperature with a residence time of less than 1 min in the first reactor and 10 min in the second. It was even more intriguing that generally no symmetric ketone or alcohol byproduct was observed, and in most cases, more than 70% yield was isolated. Both electron-rich and electron-deficient aromatic lithium compounds could be employed efficiently in our protocol (**5–9**). Some heteroaromatic lithium reagents appeared to be good coupling partners as well (**10–13**). Primary aliphatic lithium species generally reacted effectively in the flow system, no matter whether they were introduced in the first or the second step (**14–16**, **18–21**). Functionalities such as alkene (**19**), alkyne (**20**), and silane (**21**) were all tolerated. Secondary lithium reagents such as the cyclopropyl lithium (**22**) were also suitable substrates. Notably, most of these ketone products are difficult to access through Friedel–Crafts acylation[16] and these representative examples illustrate the broad applicability of flow systems for the synthesis of substituted ketones. To further demonstrate the robustness of our systems, we were able to run experiments for 5 h without any interruption to collect products **5** (1.71 g, 88% yield) and **9** (2.26 g, 82% yield). Importantly, due to the significantly reduced amount of CO_2 compared to batch conditions, our flow method would be ideal for the utilization of expensive $^{13}CO_2$ or $^{14}CO_2$ gas in the preparation of isotope-labeled ketones, which are used as tracers for modeling a variety of chemical and biochemical systems.[17]

However, some limitations on using organolithium reagents in the flow systems were observed. Reactive secondary lithium compounds were prone to react with THF instead of CO_2 or the carboxylic lithium salt intermediate.[18] Some heteroaromatic lithium species such as the 2-pyridinyllithium decomposed quickly at room temperature and blocked the flow system. We surmised that use of the more stable Grignard reagents may solve these problems. As the most available and popular reagents in organometallics, Grignard reagents provide a wider substrate scope than organolithium reagents and their use should extend the range of ketone products beyond those accessible with organolithium compounds.

The carboxylation of Grignard reagents with CO_2, a classic textbook transformation, has been used in flow systems for the synthesis of carboxylic acids,[9c] avoiding the problematic formation of symmetric ketone byproducts which was observed with organolithium reagents.[19] However, the reaction between Grignard reagents and carboxylic acids or carboxylic lithium salts cannot be used directly for the synthesis of ketones in batch conditions since low yields and the simultaneous formation of alcohols are observed.[3c,20] This undesired process likely occurs as a result of the bimetallic intermediate, $R^1R^2C(OMgX)(OM)$, being more prone than the corresponding dilithium intermediate to form the free ketone prior to hydrolysis.[3c]

Relying upon the greater kinetic control of the flow system, we envisioned that the generated unstable bimetallic intermediate would be quenched efficiently and faster than the conversion to byproducts would occur. We were pleased to discover that the flow procedure can be successfully applied to synthesize diaryl (**25**), aryl–alkyl (**5**, **23**, **24**, **29**), vinyl–alkyl (**26**), and alkyl–alkyl (**15**, **27**, **28**) ketones in good yields (Table 3). In all cases, the alcohol byproducts were observed in less than 10%, probably due to the mild conditions (room temperature) and short reaction time (10 min). Although the reaction rate of lithium addition to carboxyl magnesium was generally lower than that of carboxyl lithium intermediates, the rate was significantly enhanced by using only Et_2O as the solvent.[21] More importantly, ketones with secondary alkyl substituents (**27–29**) can be produced effectively by this approach, which complements the scheme based solely on organolithium reagents. To the best of our knowledge, our flow synthesis presents the first example of a direct synthesis of ketones exhibiting a general substrate scope and good selectivity that involves Grignard reagents without any additives.[22] We also tested the Grignard reagent/CO_2/Grignard reagent sequence in the flow system (**30**). It required a higher temperature (30°C) and longer reaction time (30 min) to achieve a good conversion (70% for the second step), however, the alcohol byproduct was significantly increased (approximately 20%).

Having demonstrated the efficient generation of ketones from organolithium or organomagnesium reagents, we realized that the introduction of another flow component for the on-demand, in-line generation of organolithium or organomagnesium intermediates before the carboxylation with CO_2

Table 3: Flow synthesis of ketones starting with Grignard reagents.[a]
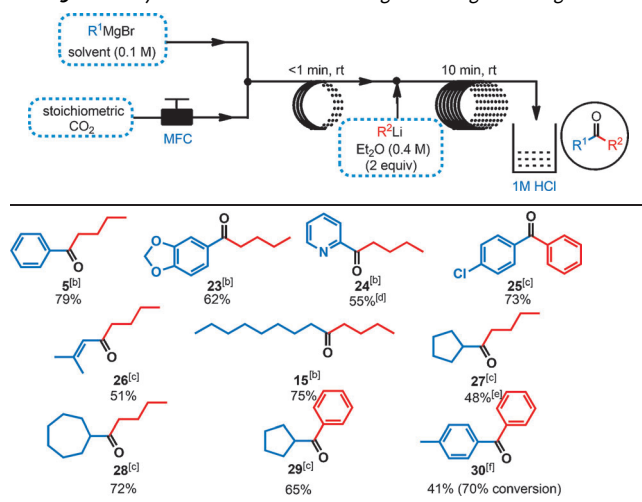
[a] Productivity: (0.04 mmol min^{-1}) × yield [%]. [b] THF was used as solvent for Grignard reagents. [c] Et$_2$O was used as solvent for Grignard reagents. [d] Ultrasonic irradiation was used to prevent clogging of reactor. [e] Product volatility diminished the yield. [f] The TolMgBr/CO$_2$/PhMgBr sequence was used, see the Supporting Information.

would provide a more efficient overall process to prepare ketone products.[23,24] We thus examined the organometallic generation/carboxylation/lithium addition sequence in an integrated flow system. As shown in Table 4, the continuous flow system was effective for exothermic reactions such as lithium–halogen exchange, lithiation, and magnesium–halogen exchange due to fast mixing and efficient heat transfer. Thus this three-step continuous process proved to be a more convenient and effective protocol for the smooth generation of ketones.

In summary, two complementary continuous flow systems (using either stoichiometric or excess CO$_2$) have been developed for an efficient synthesis of ketones with a variety of substitution patterns through an organolithium/CO$_2$/organolithium sequence at ambient temperature and pressure. The merits of flow systems over batch conditions provide a much more convenient protocol with almost complete suppression of the formation of undesired symmetric ketones or tertiary alcohol byproducts. The observation that in this reaction organolithium reagents were more reactive in Et$_2$O than in THF was unprecedented as far as we are aware, and the first synthesis of ketones from the Grignard/CO$_2$/organolithium sequence was also developed in this study. By integrating an in-line generation of organolithium or organomagnesium species, a telescoped one-flow process capable of preparing ketones in a modular fashion from simple precursors has thus been established.

Table 4: Integrated three-step continuous-flow synthesis of ketones.

Entry	R^{1}X	Organometallic compound	CO$_2$ (equiv)	T [°C]	t [min]	Yield [%][a]
1		nBuLi (1.05 equiv)	1.05	0	1	84
2		nBuLi (1.05 equiv)	1.05	rt	15	79
3		iPrMgCl·LiCl (1.05 equiv)	1.05	rt	15	72

[a] Yield of the isolated product. Productivity: (0.04 mmol min^{-1}) × yield [%].

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