

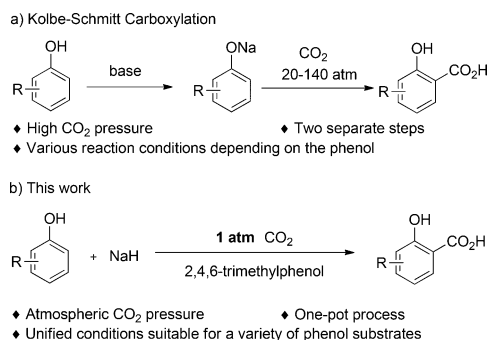
Carboxylation

Carboxylation of Phenols with CO₂ at Atmospheric PressureJunfei Luo,^[a, b] Sara Preciado,^[b] Pan Xie,^[a] and Igor Larrosa*^[a]

Abstract: A convenient and efficient method for the *ortho*-carboxylation of phenols under atmospheric CO₂ pressure has been developed. This method provides an alternative to the previously reported Kolbe–Schmitt method, which requires very high pressures of CO₂. The addition of a trisubstituted phenol has proved essential for the successful carboxylation of phenols with CO₂ at standard atmospheric pressure, allowing the efficient preparation of a broad variety of salicylic acids.

The formation of C–C bonds to build complexity from available chemical feedstocks is a fundamental goal of organic chemistry.^[1] In this regard, the development of methodologies for the transformation of CO₂, a green carbon source that is highly abundant in the atmosphere as well as non-toxic, into valuable organic compounds is of great interest.^[2] A simplest such reaction is the formation of carboxylic acids by carboxylation of organic molecules with CO₂. Numerous methodologies have been developed for the carboxylation of different organometallic reagents in the past.^[3] More recently, a breakthrough on the transition-metal-catalysed reductive carboxylation of readily available starting materials, such as aryl or benzyl halides and phenol derivatives, has provided an alternative for the synthesis of carboxylic acid derivatives.^[4] Similarly, the development of direct C–H carboxylation methods has also been of great interest due to their significance from a step- and atom-economical point of view.^[5]

The Kolbe–Schmitt reaction is one of the most important and well-known carboxylation reactions, providing direct access to salicylic acids by the *ortho* C–H carboxylation of phenoxides with CO₂ (Scheme 1 a).^[6] Salicylic acids are important motifs in pharmaceuticals, agrochemicals, advanced materials, as well as important intermediates in organic synthesis.^[7] Owing to the low cost of such method, the Kolbe–Schmitt reaction is widely used in industry, most notably for the synthesis of aspirin.^[8] However, this process still presents some draw-



Scheme 1. Carboxylation of phenols.

backs, which can make its application difficult in some laboratories: 1) High CO₂ pressure (20–100 atm) and temperature (130–280 °C) are generally required to achieve good conversion. Even though one and a half centuries have passed since the original reports, no method has been reported for the efficient carboxylation of phenols proceeding under atmospheric CO₂ pressure; 2) The preparation and isolation of completely dry phenoxide from the corresponding phenol is necessary, as the presence of water inhibits the Kolbe–Schmitt carboxylation;^[9] 3) Conditions vary over a wide range of pressures, temperatures and reaction times, depending on the phenol used.^[10]

Herein, we report the first example of the Kolbe–Schmitt carboxylation that is able to proceed efficiently at atmospheric CO₂ pressure for a variety of phenol substrates. We found that using 2,4,6-trimethylphenol as a recyclable additive proved key for this carboxylation, significantly increasing the initial reaction rate as well as improving the final yield of the carboxylation. This method provides a straightforward access to salicylic acids by avoiding the isolation of the phenoxide and the requirement of high-pressure reaction equipment. Moreover, unlike the classic Kolbe–Schmitt method, in which the conditions significantly vary for different starting materials, our method allows the transformation of a variety of phenols into the corresponding salicylic acids in good yields under unified conditions (Scheme 1 b).

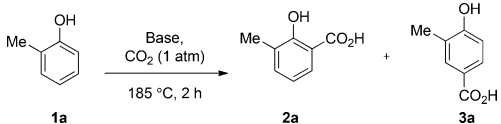
We started our investigation by studying the carboxylation of *o*-cresol (**1 a**) with 1 atm of CO₂ at 185 °C in the absence of solvent (Table 1). A screening of bases revealed that neither NaOH nor KOH, the two most commonly used bases in the Kolbe–Schmitt reaction, led to any reactivity in a one-pot process without the isolation of the phenoxide intermediate (entries 1 and 2). Alkali-metal carbonates have also been reported to be useful bases in the Kolbe–Schmitt reaction.^[11] However,

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Table 1. Screening of bases.^[a]



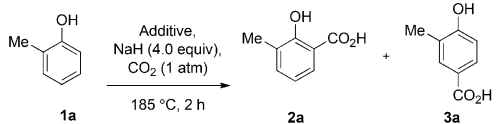
Entry	Base (equiv)	Yield 2a [%]	Yield 3a [%]
1	KOH (1.0)	0	0
2	NaOH (1.0)	0	0
3	K ₂ CO ₃ (1.0)	1	0
4	Na ₂ CO ₃ (1.0)	0	0
5	NaH (1.0)	32	2
6	NaH (2.0)	38	2
7	NaH (3.0)	39	3
8 ^[b]	NaH (2.0)	39	2

[a] Reactions were carried out with 0.25 mmol of **1a**. The mixture was initially heated at 100 °C for 5 min in order to form the potassium or sodium 2-methylphenolate, following by heating at 185 °C under CO₂ atmosphere; yields were determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] The reaction was carried out for 4 h.

only 1% of the desired product **2a** was obtained when K₂CO₃ was employed (entry 3) and no product was observed when using Na₂CO₃ (entry 4). Finally, NaH was chosen so as to avoid the formation of water during the deprotonation of *o*-cresol (**1a**). Gratifyingly, 32% of *ortho*-carboxylated product **2a** and 2% of *para*-carboxylated product **3a** were obtained when one equivalent of NaH was used (entry 5). Doubling the amount of NaH to two equivalents increased the yield to 38% (entry 6). However, a further increase in the amount of NaH (entry 7) afforded no further improvement in the yield. Finally, prolonged reaction times did not increase conversion (entry 8).

It has been proposed that CO₂ could be captured by a metal phenolate through weak coordination between the alkali metal and CO₂.^[12] We therefore speculated that the carboxylation could be promoted by the use of an additional “supporting” phenolate, through an increased CO₂ absorption. However, this phenolate should not be able to undergo carboxylation itself so as to avoid the consumption of the absorbed CO₂. Thus, we set on investigating whether 2,4,6-trisubstituted phenolates, with their *ortho*- and *para*-positions blocked, would be suitable additives for this purpose (Table 2). Gratifyingly, an improvement in the yield was obtained by the addition of one equivalent of 2,6-di-*tert*-butyl-4-methoxyphenol (**4**), in the presence of four equivalents of NaH, affording 53% of the desired *ortho*-carboxylated product **2a** and 5% of *para*-carboxylated product **3a** (entry 2). Encouraged by this result, substituted phenols **5** and **6** with *tert*-butyl at both *ortho*-positions were tested but no improvement in the yield was observed (entries 3 and 4). The more electron-deficient 2,4,6-trifluorophenol (**7**) afforded a similar result (entry 5). Gratifyingly, the electron-rich but less sterically hindered 2,4,6-trimethylphenol (**8**) led to a significant improvement in the yield, with a total of 94% carboxylation and an 82% of **2a** (entry 6). Further efforts towards reducing the amount of phenol additive **8** or NaH, and the temperature led to lower yields (entries 7–9). The previous

Table 2. Screening of phenol additives.^[a]



Entry	Additive (equiv)	Yield 2a [%]	Yield 3a [%]
1 ^[b]	–	38	2
2	4 (1.0)	53	5
3	5 (1.0)	37	3
4	6 (1.0)	36	2
5	7 (1.0)	40	5
6	8 (1.0)	82	12
7	8 (0.5)	76	11
8 ^[c]	8 (1.0)	74	11
9 ^[d,e]	8 (1.0)	62	10

[a] Reactions were carried out with 0.25 mmol of **1a**. The reaction mixture was heated at 100 °C for 5 min in order to form sodium phenoxides before heating at 185 °C under CO₂ atmosphere; yields were determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] 2.0 equiv of NaH was used. [c] 3.0 equiv of NaH was used. [d] The reaction was performed at 160 °C. [e] Extending the reaction time to 3 h showed no improvement in yield.

report of the carboxylation of **1a** required 80–140 atm of CO₂ to afford 70% yield.^[10a]

In order to evaluate the magnitude of the effect of adding 2,4,6-trimethylphenol (**8**), we studied the kinetic profile of the carboxylation in the presence and absence of this additive (Figure 1). It was found that the carboxylation is rapid at the beginning of the reaction with a significant decrease in reaction rate after 1 h. The addition of **8** significantly increases the initial reaction rate as well as improving the final yield of the carboxylation, indicating that 2,4,6-trimethylphenol (**8**) plays an important role in facilitating the carboxylation reaction.

Having found suitable conditions for an atmospheric pressure Kolbe–Schmitt carboxylation, a variety of substituted phenols were tested to investigate the generality of this process (Scheme 2). Substrates with alkyl substituents at the *ortho*-

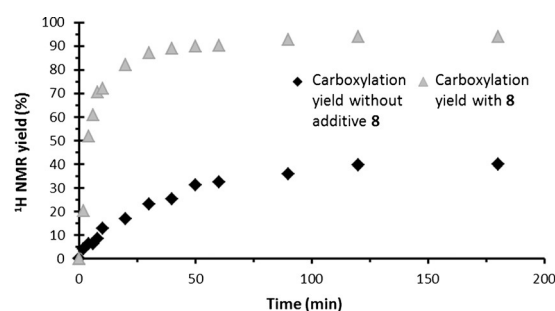
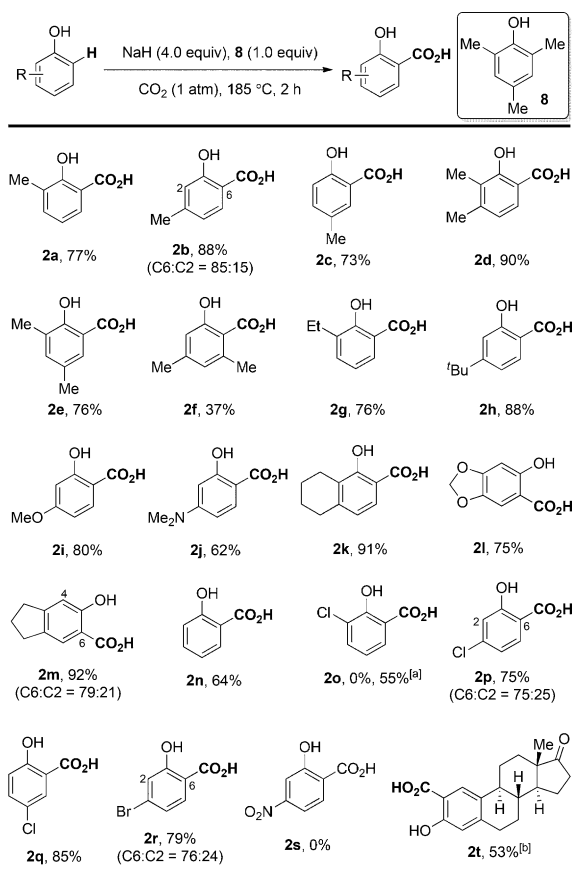


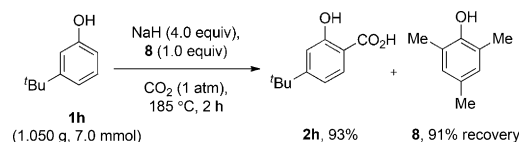
Figure 1. Kinetic profile of the carboxylation process (yield of **2a** + **3a**) in the absence (black diamonds) and in the presence (grey triangles) of one equivalent of 2,4,6-trimethylphenol (**8**).



Scheme 2. Scope of phenol carboxylation. Reactions were carried out with 0.25 mmol of phenol **1**. Yields are of the isolated pure material. [a] The reaction was carried out at 5 atm of CO₂. [b] The reaction was carried out for 16 h.

meta- and *para*-positions were all *ortho*-carboxylated in good yields (Scheme 2; **2a–h**, **2k**, **2m**), with even the highly hindered 3,5-dimethylphenol affording 37% of carboxylated product **2f**. Interestingly, with *m*-cresol (**1b**) a mixture of C6- and C2-carboxylated products in an 85:15 ratio was obtained (Scheme 2; **2b**). A similar pattern was seen with bicyclic phenol **1m** (**2m**). Conversely, increased steric hindrance at C3 prevented the formation of C2-carboxylated product **2h**. However, comparable substrates with ether substituents at the *meta*-position underwent *ortho*-carboxylation, with only one regioisomer being obtained (**2i** and **2l**). The electron-donating functionality NMe₂ was also found to be suitable in this methodology, leading to good yields (**2j**). Simple phenol was also carboxylated in good yield, affording 64% of salicylic acid (**2n**). It was gratifying that electron-withdrawing halogen groups, such as Cl and Br, at C3 and C4 were also compatible with this methodology (**2p–r**). In the case of 2-chlorophenol, a slightly higher CO₂ pressure was required for the carboxylation to proceed (**2o**). No carboxylation product was observed when a phenol containing the strongly electron-withdrawing nitro group was used (**2s**), leading to unreacted starting material. Finally, the steroid hormone estrone **1t** was found to be conveniently converted to the *ortho*-carboxylated product **2t** in 53% yield and with complete regioselectivity.

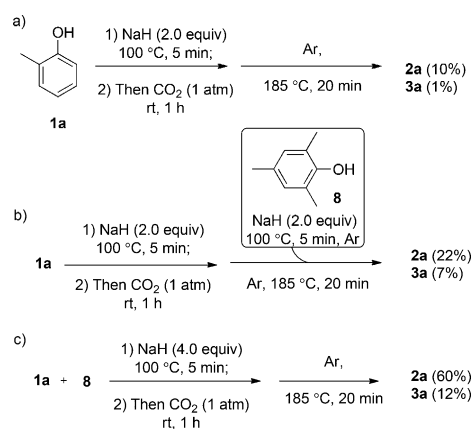
This methodology is amenable to scaling up. Applying the standard conditions, without any modification, to the *ortho*-carboxylation of 3-*tert*-butylphenol (**1h**) on a 7.0 mmol (1.05 g) scale afforded the corresponding salicylic acid **2h** in 93% yield. Importantly, the additive 2,4,6-trimethylphenol (**8**) can be easily recovered after the reaction and recycled (Scheme 3).



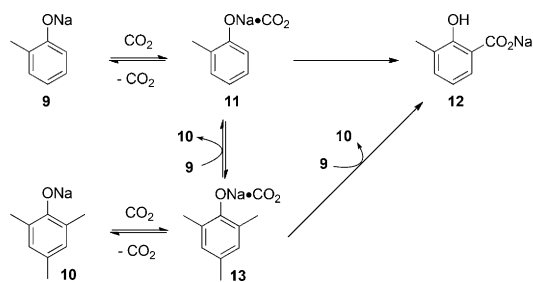
Scheme 3. Gram-scale synthesis. Yields are of isolated pure material.

We set out to further understand how 2,4,6-trimethylphenol (**8**) is able to facilitate the atmospheric pressure carboxylation reaction. Given that the carboxylation reaction would be dependent on the rate of mixing between the gas and solid phase, we hypothesized that **8** might be acting as a mixing aid, consequently promoting the carboxylation by increasing the surface area of the solid. Glass beads have been found to significantly improve the outcome of heterogeneous reactions.^[13] Thus, we tested the carboxylation of **1a** in the presence of glass beads, instead of phenol additive **8**. However, no effect on the yield of the reaction was observed, with 36% of **2a** obtained after 2 h of reaction (compare to Table 1, entry 6).^[14] This result suggests that **8** does not act as a mixing aid and instead may play a role in facilitating CO₂ fixation and delivery to the reactive phenoxide.

It is generally accepted that in the Kolbe–Schmitt reaction, monosodium salicylate (**12**) is formed by the sodium phenoxide–CO₂ complex **11** (Scheme 5).^[12, 15, 16] To probe this, we first mixed the phenol **1a** and NaH to form sodium phenoxide **9**, and then left the mixture under atmospheric CO₂ pressure at room temperature for 1 h to allow the CO₂ fixation (Scheme 4a). The CO₂ was then replaced with argon and the mixture was heated at 185 °C for 20 min, affording 10% of product **2a** and 1% of **3a**. This suggests that CO₂ is “fixed”



Scheme 4. Investigation on the effect of **8** in the absence of CO₂ atmosphere. Yields are measured by ¹H NMR using an internal standard.



Scheme 5. Mechanistic proposal for the role of 8/10.

(absorbed or adsorbed) by the solid reagents, and that this fixed CO₂ is reactive in the carboxylation conditions. In fact, it has previously been suggested that only the fixed CO₂ is reactive in the carboxylation step, not the gaseous CO₂.^[12] We set up a similar reaction, in which a mixture of **8** and NaH was added under argon after the mixture of **1a** and NaH had been exposed to CO₂ (Scheme 4b). An improvement in the yield was seen, with 22% of **2a** and 7% of **3a** being obtained after heating the mixture for 20 min. The addition of excess NaH without **8**, on the other hand, did not improve the yield.^[14] This suggests that **10**, formed by pre-mixing **8** with NaH, increases the rate of the carboxylation from **11**. Finally, we mixed both **1a** and **8** with excess of NaH, and then exposed the mixture under atmospheric CO₂ pressure at room temperature for 1 h, followed by replacement of CO₂ with argon and heated the mixture (Scheme 4c). In this case, a significantly improved yield was seen, with 60% of **2a** and 12% of **3a** being obtained. This suggests that in addition to increasing the rate of the carboxylation from **11**, species **10** also increase the amount of fixed CO₂.

We propose that the primary role of **10** may be to aid CO₂ fixation, increasing the amount of CO₂ able to react in the carboxylation step.^[17] Since **10** has both its *ortho*- and *para*-positions blocked, it is not able to undergo carboxylation with the bound CO₂. This fixed CO₂ can therefore only react with **9**, either by exchange to form **11** with subsequent intramolecular carboxylation, or by reacting directly with **9** in an intermolecular fashion (Scheme 5).

In conclusion, we have developed the first version of the Kolbe–Schmitt carboxylation, which occurs efficiently under an atmospheric pressure of CO₂. This method allows the synthesis of a variety of salicylic acids with a range of functionalities in a one-pot process without the isolation of the phenoxide precursor. It represents an improvement in terms of safety and operational simplicity over the current Kolbe–Schmitt methodologies. The additive, 2,4,6-trimethylphenol, has been suggested to act as an aid for CO₂ capture. A detailed mechanism of the carboxylation from absorbed CO₂ is the subject of further study in our group.

Experimental Section

In the glove box, NaH (60% dispersion in mineral oil, 40 mg, 1.0 mmol, 4.0 equiv) was added to a vial containing the phenol substrate (0.25 mmol) and 2,4,6-trimethylphenol (34 mg,

0.25 mmol, 1.0 equiv). The resulting mixture was heated at 100 °C for 5 min, cooled down to room temperature and grinded to powder with the use of a spatula. The vial with the mixture was taken out from the glove box, purged with CO₂ and reacted with a balloon filled with CO₂ at 185 °C for 2 h. After this time, the reaction mixture was cooled to room temperature, carefully quenched with H₂O (5 mL), acidified to pH 4 with aq. HCl (1 M), and then extracted with EtOAc (3 × 10 mL). The organic layers were dried over anhydrous MgSO₄, evaporated to dryness and purified by column chromatography to afford the corresponding salicylic acid.

Note: The reaction can be set up without the use of a glove box. In this case, the grinding of the mixture should be carried out under a stream of N₂ or Ar. Furthermore, we found that the NaH reagent does not age well, and yields decrease after prolonged use if handled outside the glove box.

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Keywords: carbon dioxide · Kolbe–Schmitt reaction · phenols · salicylic acids · synthetic methods

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