Synthetic Methods

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Continuous-Flow Synthesis of Functionalized Phenols by Aerobic Oxidation of Grignard Reagents**

*Zhi He and Timothy F. Jamison**

Abstract: *Phenols are important compounds in chemical industry. An economical and green approach to phenol preparation by the direct oxidation of aryl Grignard reagents using compressed air in continuous gas-liquid segmented flow systems is described. The process tolerates a broad range of functional groups, including oxidation-sensitive functionalities such as alkenes, amines, and thioethers. By integrating a benzyne-mediated in-line generation of arylmagnesium intermediates with the aerobic oxidation, a facile three-step, one-flow process, capable of preparing 2-functionalized phenols in a modular fashion, is established.*

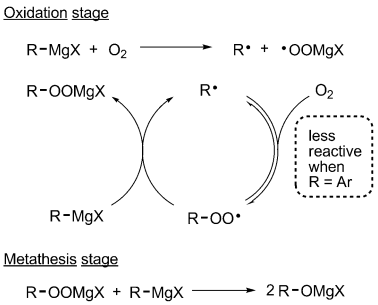
Phenols are important structural motifs which are widely present in agrochemicals, pharmaceutical products, and naturally occurring compounds.[1] As such, efficient preparation of phenols is of great significance to several fields within the chemical, biological, and materials sciences.

In laboratory or industrial fine-chemical production, functionalized phenols are usually prepared by either traditional nucleophilic aromatic substitution[2] or oxidative methods using aryl boronic acids/esters.[3] Hydroxylation of aromatic derivatives with transition-metal catalysis has also emerged as an attractive alternative for the synthesis of phenols in recent years.[4] However, applications of these methods are constrained by harsh reaction conditions, limited functional-group tolerance, or high costs and toxicity as a result of the use of transition-metal catalysts and sophisticated ligands. Consequently, preparation of functionalized phenols in a mild, economical, and green manner still constitutes a significant challenge.

In this regard, we herein report the development of phenol synthesis by direct aerobic oxidation of aryl Grignard regents with compressed air in continuous gas-liquid segmented flow systems.[5] By way of the method we developed, a wide range of substituted phenols can be easily obtained. In addition, by incorporating an in-line generation of functionalized arylmagnesium species, from benzyne intermediates, before the aerobic oxidation process, a facile three-step one-flow preparation of *ortho*-functionalized phenols in a modular fashion has been realized. This method complements the existing ones described above and highlights several of the most advantageous aspects of synthesis under continuous-flow conditions, including, superior gas-liquid mixing, efficient heat transfer, and the use of reagents and intermediates whose very high reactivity would otherwise be limiting or prohibitive, in this case O_2 (compressed air) and benzyne derivatives.

Given the fact that alkyl Grignard reagents easily undergo oxidation with molecular O_2 to yield alcohols,[6] the analogous transformation using arylmagnesium species is envisioned as an appealing approach to access phenols. With regard to green synthesis, this approach is particularly attractive given the use of molecular O_2 as an inexpensive and sustainable oxidant, the absence of precious or toxic transition-metals and ligands, the easy access of functionalized arylmagnesium reagents,[7] as well as the step economy compared to boronic acid/ester oxidation. However, while high yields of alcohols (60–90%) are usually obtained from alkyl Grignard reagents during the aerobic oxidation using pure O_2, aryl substrates remain problematic in that poor yields of phenols (10–20%) are afforded along with a complex mixture of byproducts.[8]

A two-stage reaction sequence involving a radical chain process is believed to take place during the oxygenation of Grignard reagents (Scheme 1).[9] An alkyl or aryl radical is



Scheme 1. Proposed mechanism for oxidation of Grignard reagents with O_2.

first generated from the initial interaction between organomagnesium species and molecular O_2. The carbon-centered radical intermediate is then trapped by another O_2 to form an organoperoxide radical which in turn reacts with a second Grignard molecule to create an organoperoxide magnesium salt, which ultimately provides the formation of alkoxide or phenoxide products. It is believed that, compared to alkyl radicals, aryl radicals formed from the arylmagnesium species are intrinsically much less reactive towards O_2,[10] thereby

[*] Dr. Z. He, Prof. Dr. T. F. Jamison
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
E-mail: tfj@mit.edu

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generating byproducts by undesired radical coupling or hydrogen abstraction with substrates or solvent molecules.

We hypothesized that increasing the concentration and mass transfer of O_2 in the solution would comprise a tactic that would overcome the reactivity challenge between aryl radicals and molecular O_2. Given the fact that continuous-flow reactors have been proven to be more efficient than conventional batch systems for biphasic gas-liquid reactions because of the improved interphase contact, surface-to-volume ratio, as well as the rate of mass and heat transfer,[11] we envisioned that flow chemistry would be an advantageous format for reactions between aryl Grignard reagent solutions and molecular O_2.[12]

We initially tested the reaction of commercial phenylmagnesium bromide solution in tetrahydrofuran (THF) with pure O_2 gas in a simple flow set-up consisting of a perfluoroalkoxyalkane (PFA) tubing reactor coil (300 cm, ID 0.03") and a polyetheretherketone (PEEK) Y-mixer, which was connected to the oxygen gas cylinder and a stainless steel syringe containing the Grignard reagent solution (Figure 1a).

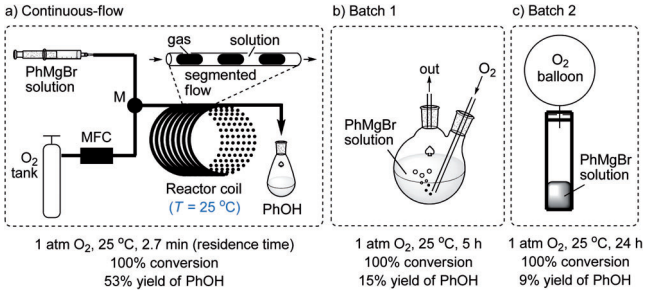


Figure 1. Comparison of continuous-flow results with those obtained from macrobatch conditions. M = PEEK Y-mixer. Yield is that of phenol isolated after silica gel chromatography.

The O_2 gas was metered into the system using a mass flow controller (MFC), and the Grignard reagent solution (0.2 M) was infused by using a syringe pump. A gas-liquid segmented flow was generated in the tubing reactor coil after the liquid and gas streams met together through the Y-mixer. To our delight, by employing ambient conditions (25 °C, 1 atm) with a 1.5:1 *v*/*v* ratio of O_2 gas (0.3 mL min^{-1}) to the Grignard reagent solution (0.2 mL min^{-1}), a 53% yield of phenol was observed within a residence time (t_R) of 2.7 minutes. This was in sharp contrast to the results obtained from macrobatch reactions. While a stream of O_2 (0.3 mL min^{-1}) was bubbled through the Grignard reagent (25 mL, 0.2 M) in a 50 mL round-bottom flask under the same temperature and pressure for 5 hours (Figure 1b), only a 15% yield of phenol was isolated. The generation of phenol further decreased to 9% when a test tube (8 cm × ID 1.3 cm) containing the reaction solution (5 mL, 0.2 M) was simply equipped with an O_2 balloon and stored at 25 °C for 24 h (Figure 1c).

The improved result of the reaction between PhMgBr and pure O_2 gas under flow conditions encouraged us to consider using air as a more economical and safer source of oxidant. We anticipated that cryogenic conditions with pressurized air would be beneficial for the selectivity and conversion of the

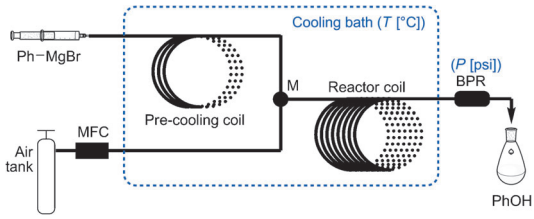


Figure 2. Continuous-flow set-up for the phenol generation by aerobic oxidation.

oxidation. Accordingly, a new flow set-up equipped with a pre-cooling PFA tubing coil and a backpressure regulator (BPR) was constructed (Figure 2), thus aiming to control the temperature and pressure in the system. In addition, as a way of compensating for a possible low reactivity of air, the modified reaction system utilized a longer PFA tubing reactor (600 cm, ID 0.03") and a higher gas/liquid ratio (3:1 *v*/*v*) for the segmented flow generation (see the Supporting Information for details).

By applying these flow settings, we thus evaluated the aerobic oxidation of PhMgBr with dry air under a series of temperatures and pressures. The results are summarized in Figure 3, in which the yields of phenol were plotted against temperature and pressure in the tubing reactor (residence

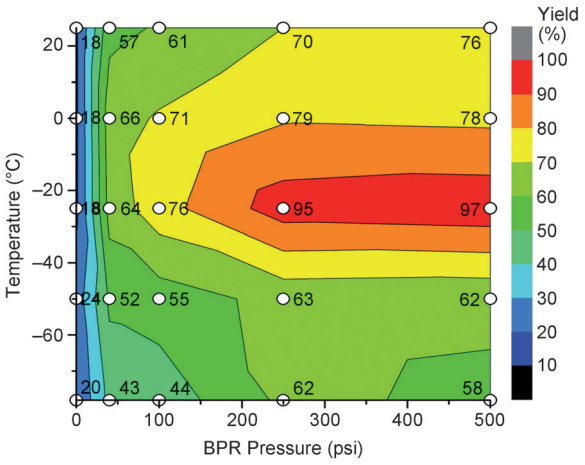
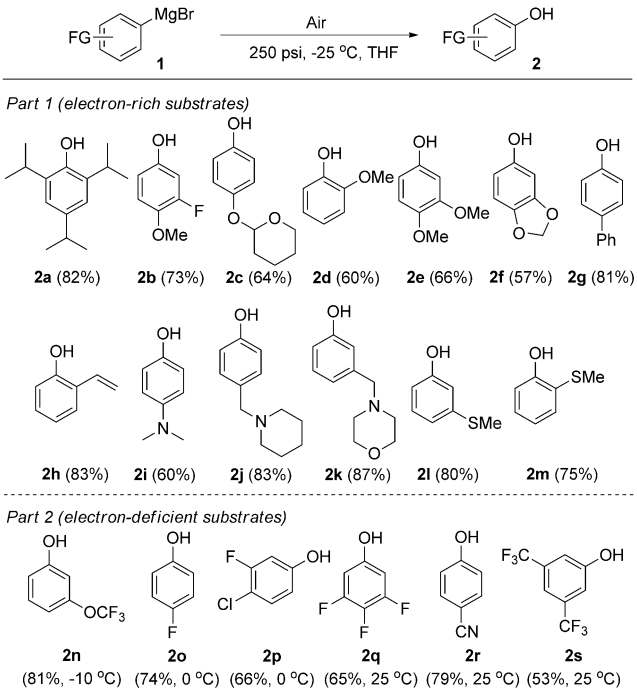


Figure 3. Effect of temperature and pressure on the yield (GC) of phenol in the aerobic oxidation of phenylmagnesium bromide in THF.

time t_R = 3.4 min) as a contour map with a scattered overlay. As expected, high pressure of air indeed facilitated the formation of phenol. The outcomes of the reaction also significantly depended on temperature. A high-yielding region with nearly quantitative generation of phenol was found under a pressure of more than 200 psi at around −25 °C. Decreased yields were observed with elevated temperature, and could be attributed to the increase of side reactions. In contrast, lowering the temperature also resulted in poor yields because of the low conversion of the starting organomagnesium reagent.

With the reaction profile in hand, we proceeded to examine the generality of the aerobic phenol preparation with a range of substituted phenylmagnesium bromides in a THF

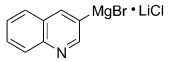
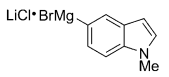


Scheme 2. Preparation of functionalized phenols by aerobic oxidation of Grignard reagents. Unless otherwise noted, the reactions were carried out with arylmagnesium bromide in THF solution and compressed air under 250 psi backpressure at −25 °C, $t_R = 3.4$ min. All yields in parentheses are yields of isolated products after silica gel chromatography.

solution by using the same flow setup pictured in Figure 2. As expected, substrates with electron-donating groups (Scheme 2a) generally worked well under the optimal reaction conditions (−25 °C, 250 psi air) to provide good yields of phenol products over the 3.4 minutes of residence time (t_R). In contrast, electron-deficient phenylmagnesium regents (Scheme 2b) were found less reactive towards the oxidation, and thus higher reaction temperatures (−10 to 25 °C) were employed to afford full conversion and comparable yields of phenols within the same residence time. It is intriguing that varieties of oxidation-sensitive functional groups were found to be tolerant towards the continuous-flow process. In particular, functionalities such as alkenes (**2h**), anilines (**2i**), and tertiary amines (**2j**,**k**) all survived the reaction. Moreover, to our surprise, thiol ethers (**2l**,**m**) also escaped the oxidation. These representative examples illustrate the broad applicability of functionalized phenol synthesis by the aerobic oxidation of substituted phenylmagnesium reagents.

Encouraged by the above-mentioned results, we extended our investigations to heteroarylmagnesium reagents (Table 1). The outcome of the reaction was found to be highly dependent on the structure and the electronic property of the heteroaromatic ring. While poor yields of oxidation products were obtained from thiophene-based organomagnesium reagents (entries 1 and 2), substrates equipped with the magnesiated pyridine rings generally gave much better results (entries 3 and 4). In addition, the indole-derived organomagnesium reagent **3e** was also tested in the aerobic oxidation (entry 5). Under the standard reaction conditions

Table 1: Aerobic oxidation of heteroarylmagnesium reagents.[a]

Entry	Heteroarylmagnesium reagents		Product		Yield [%][b]
1		**3a**		**4a**	24
2		**3b**		**4b**	32
3		**3c**		**4c**	86
4		**3d**		**4d**	47
5[c]		**3e**		**4e**	70

[a] Unless otherwise noted, the reactions were carried out with heteroarylmagnesium bromide in THF solution and compressed air under 250 psi backpressure at 25 °C, $t_R = 3.4$ min. [b] Yields of products isolated after silica gel chromatography. [c] The reaction was carried out at −25 °C.

(−25 °C, 250 psi air), the corresponding 5-hydoxyindole product **4e** was successfully obtained in a good yield.

Having demonstrated the efficient generation of phenols from commercial or preformed Grignard reagents using a single continuous-flow reactor, we envisioned that incorporating another flow system, which is capable of in-line generation of organomagnesium intermediates before the aerobic oxidation step, would provide a more convenient way to obtain functionalized phenols. We investigated a benzyne approach to generate the *ortho*-substituted organomagnesium intermediates, and it involves a selective addition of magnesiated nucleophiles to the benzyne intermediate formed from 1,2-dihalobenzenes through a magnesium–halogen exchange/elimination process.[13] To the best of our knowledge, preparation of functionalized Grignard regents by such an approach using continuous-flow systems has not been reported.[14,15]

We thus examined the organomagnesium generation/oxidation sequence in an integrated flow system which consists of two PEEK T-mixers (M1, M2), one PEEK Y-mixer (M3), three PFA tubing reactors (R1, R2, and R3), and a pre-cooling PFA tubing coil, as shown in Figure 4. The first step of the synthesis was the deprotonation of nucleophiles with excess isopropylmagnesium chloride lithium chloride complex (*i*PrMgCl·LiCl)[16] in M1 and R1 at 25 °C (T_1). The resulting mixture was merged with a stream of 1,2-dihalobenzenes in a THF solution in M2 and R2 under an elevated temperature 80–120 °C (T_2) for the in situ benzyne formation and nucleophilic addition, thereby generating the desired functionalized arylmagnesium intermediate. Passing through a check-valve, the reaction solution entered the same flow system previously described for cryogenic aerobic oxidation (Figure 2). The reaction solution was thus quickly cooled to −25 °C (T_3) in the pre-cooling coil and subsequently combined with a stream of compressed air in M3 and R3 under the pressure of 250 psi to yield the final phenol products.

Different heteroatomic nucleophiles were subjected to the integrated flow system to obtain a range of *ortho*-

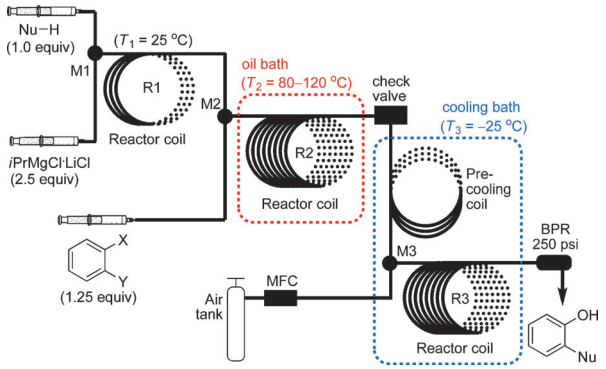
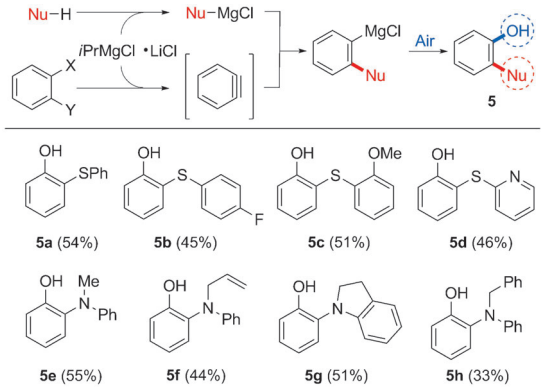


Figure 4. Integrated three-step continuous-flow system for the preparation of *ortho*-functionalized phenols. M1 and M2 = PEEK T-mixers, M3 = PEEK Y-mixer.

functionalized phenols. The results are summarized in Scheme 3. By utilizing inexpensive 1,2-dibromobenzene as the benzyne precursor at 80 °C, a variety of substituted thiophenols smoothly generated 2-(arylthio)phenylmagnesium intermediates in the reactor R2. After the subsequent aerobic oxidation, the corresponding 2-(arylthio)phenol products (**5a**–**c**) were successfully obtained in moderate yields, upon isolation, over the three-step continuous process within a total linear residence time (t_R) of 14 minutes. Under the same reaction conditions, substrates with heterocycles such as pyridin-2-thiol also smoothly afforded the desired 2-(pyridinyl)thiophenol **5d** with the pyridine ring intact.



Scheme 3. Synthesis of *ortho*-functionalized phenols by the integrated flow system. Total linear residence time t_R = 14 min. All yields in parentheses are yields of products isolated after silica gel chromatography.

We have also examined the reactivity of nitrogen nucleophiles in the hope of obtaining 2-aminophenols. Gratifyingly, aniline derivatives with N-alkyl substituents successfully afforded the desired phenol products (**5e**–**h**; Scheme 3) in moderate yields. It is noteworthy that, while *N*-methyl aniline and indoline generated 2-aminophenylmagnesium intermediates in reactor R2 efficiently with 1,2-dibromobenzene at 80 °C, more sterically hindered N-allyl or benzyl substrates required a higher reaction temperature (120 °C) and the use of a more energy-demanding benzyne precursor, that is, 1-bromo-2-chlorobenzene (see the Supporting Information for details).

In summary, we have demonstrated a mild, efficient, and economical way of preparing functionalized phenols with excellent functional-group compatibility by the oxidation of aryl Grignard reagents with compressed air in continuous-flow systems. By integrating a benzyne-mediated in-line generation of arylmagnesium species with the aerobic oxidation, a convenient three-step one-flow process capable of preparing 2-functionalized phenols in a modular fashion was established.

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