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# Microfluidic Synthesis of *tert*-Butyl Peresters via KI-Catalyzed Oxidative Coupling of Methyl Arenes and *tert*-Butyl Hydroperoxide

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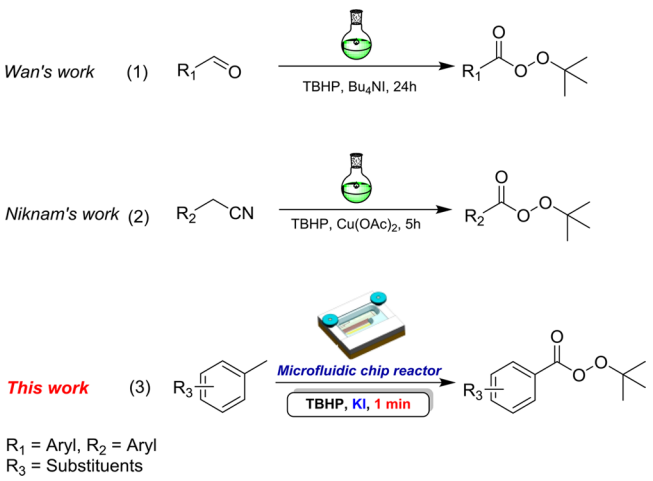
Supporting Information

**ABSTRACT:** A green and efficient organic−aqueous two-phase reaction route for the synthesis of *tert*-butyl peresters by KI-catalyzed C−H oxidation of methyl arenes in a microfluidic chip reactor has been developed. Moreover, a series of *tert*-butyl perester products were obtained in moderate to good yields under metal-free conditions. A scale-up continuous flow system was constructed to verify the application of this method.

## INTRODUCTION

*tert*-Butyl peresters, common core organic compounds, play an important role in organic synthesis.[1] Traditionally, *tert*-butyl peresters were obtained by utilizing carboxylic acid and its derivatives with TBHP (*tert*-butyl hydroperoxide).[2] In 2011, Wan's group reported a novel method for the synthesis of *tert*-butyl peresters from aldehydes which is distinguished by high atom economy and being base-free (Scheme 1, eq 1).[3] Wang's group discovered a TBAI (tetrabutylammonium iodide)-catalyzed oxidation of alcohols to prepare *tert*-butyl peresters at room temperature in an aqueous system.[4] Transition metals are of significance in these transformations, which might provide a chance for formation of C−H, C−N, C−O bonds via cross-dehydrogenative coupling (CDC) reactions.[5] Recently, Niknam's group developed a copper-catalyzed oxidative coupling of benzyl cyanides with TBHP to synthesize *tert*-butyl peresters under solvent-free conditions (Scheme 1, eq 2).[6] However, these methods mentioned above still have some apparent drawbacks. It is hard to enhance the mixing efficiency of the organic−aqueous two-phase reactions in a batch reactor. Although extending the reaction time might improve the yield, the quality and stability of the desired product could not be maintained. Furthermore, safety risks existed in the conventional scale-up batch reaction for the synthesis of peresters.

**Scheme 1. Microfluidic Synthesis of *tert*-Butyl Peresters *via* KI-Catalyzed Oxidative Coupling of Methyl Arenes and *tert*-Butyl Hydroperoxide**




The microfluidic system, the emerging platform for chemical synthesis, has been developing rapidly in green chemistry.[7] Compared to traditional chemical batch reactors, microfluidic reactors possess thinner channels with dimensions of tens to hundreds of micrometers,[8] which could improve the efficiency of mass transfer and heat transfer between oil and water.[9] Besides, the state of mixing could be controlled by regulating the temperature and average flow rate precisely.[10] As a phase transfer catalyst, TBAI worked well in a previous method for the synthesis of *tert*-butyl peresters. However, the cheaper KI could not be applicable to these reactions due to the poor efficiency of the organic−aqueous two-phase reactions in a conventional batch reactor. Traditional methods for the synthesis of *tert*-butyl peresters required up to 20 h to react, while the microfluidic system merely consumed a little residence time and the product was constantly collected, which might efficiently solve the potential safety problem. Herein, we developed a novel organic−aqueous two-phase route to *tert*-butyl peresters via KI-catalyzed oxidative coupling of methyl arenes and TBHP in a microfluidic chip reactor (Scheme 1, eq 3).

## RESULTS AND DISCUSSION

Initially, a model reaction of toluene (**1a**) and TBHP (**2**) to form *tert*-butyl peresters (**3a**) in a microfluidic chip reactor was chosen as the model reaction to optimize reaction conditions

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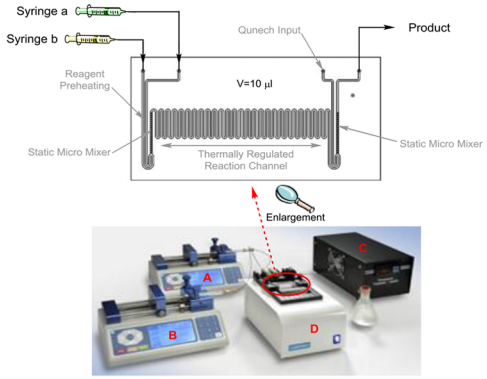
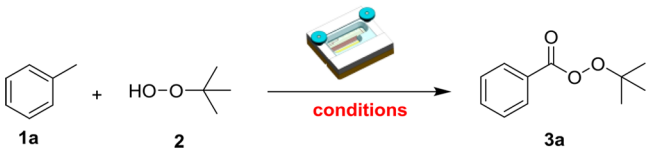
by examining a series of reaction parameters. And the results were summarized in Table 1. As shown in Table 1, the microfluidic chip reactor consisted of syringe pumps (A and B), a controller (C), and a start unit (D). The volume of syringe and chip are 1 mL and 10 μL, respectively. The reaction time can be modulated by adjusting the flow rate of syringes. Moreover, the heating device of the chip fixed on the start unit (D) was controlled by the controller (C). The use of a microfluidic chip reactor provides a medium for our reaction, which is safe, efficient, environmental friendly, and with practical application. First, a series of phase transfer catalysts, such as TBAI (tetrabutylammonium iodide), TBAB (tetrabutylammonium bromide), and TBAC (tetrabutylammonium chloride) were screened to investigate the reaction conditions (Table 1, entries 1−3), but only the TBAI obtained the higher yield (Table 1, entry 1). The reaction proceeded less efficiently in the presence of NIS (Table 1, entry 4). To our surprise, when we took advantage of inexpensive KI as the catalyst, an excellent yield of 61% was obtained within 40 s (Table 1, entry 5). Furthermore, the temperature was also tested (Table 1, entries 6−8). However, both raising the temperature to 60 °C and lowering the temperature to rt (room temperature) failed to improve the yield. In order to improve the yield of the product **3a**, the residence time in the chip reactor was screened (Table 1, entries 9−13). The range of corresponding flow rate of syringe A and B was adjusted from 3.75 to 10 μL/min. And the optimal residence time was 60 s (Table 1, entry 11). From Table 1, it is easy to determine that extending the residence time further could not improve the yield efficiently. When a smaller volume (5 μL) of chip was utilized, a lower yield of desired product **3a** was obtained (Table 1, entry 14). As shown in Figure 1, a group of experiments in batch and chip were completed, respectively. As the reaction time went on, the yield of **3a** was able to slightly increase in batch, with the best yield being just 40%. Meanwhile, a yield of 81% was obtained under the optimal reaction conditions in chip, which was a great breakthrough. However, a longer residence time results in a smaller average velocity in a fixed reactor and leads to weaker mass transfer in the continuous flow system, which could explain the phenomenon that extending the residence time reduced the reaction yield. These results clearly indicated that the reaction with KI as the catalyst in the chip reactor performs better than that in batch because the microfluidic chip reactor could provide efficient mixing to enhance mass transfer and heat transfer between the aqueous and organic phases.

With the optimized conditions in hands, a variety of toluene derivatives **1** were chosen to react with TBHP **2** to synthesize the homologous products **3** in a microfluidic chip reactor. The

**Table 1. Optimization of Reaction Conditions**[a]




1a 2 3a

| entry | catalyst | $T$ (°C) | time (s) | yield (%)[b] |
|---|---|---|---|---|
| 1 | TBAI | 40 | 40 | 62 |
| 2 | TBAB | 40 | 40 | <5 |
| 3 | TBAC | 40 | 40 | <5 |
| 4 | NIS | 40 | 40 | 0 |
| 5 | KI | 40 | 40 | 61 |
| 6 | KI | rt | 40 | 50 |
| 7 | KI | 50 | 40 | 56 |
| 8 | KI | 60 | 40 | 55 |
| 9 | KI | 40 | 30 | 31 |
| 10 | KI | 40 | 50 | 69 |
| 11 | KI | 40 | 60 | 81 |
| 12 | KI | 40 | 70 | 77 |
| 13 | KI | 40 | 80 | 59 |
| 14[c] | KI | 40 | 60 | 60 |

[a]Reaction conditions: Solution A: 1 mmol of **1a** in 6 mmol of **2** (70% in $H_2O$), pumping the organic phase in syringe A (Titration of TBHP in the aqueous phase was only 0.062 mmol, which could be ignored); Solution B: 0.2 mmol of catalyst in 1 mL of $H_2O$; flow rate of syringe A = flow rate of syringe B (μL/min); the volume of chip reactor = 10 μL. [b]Isolated yield. [c]The volume of chip reactor = 5 μL.

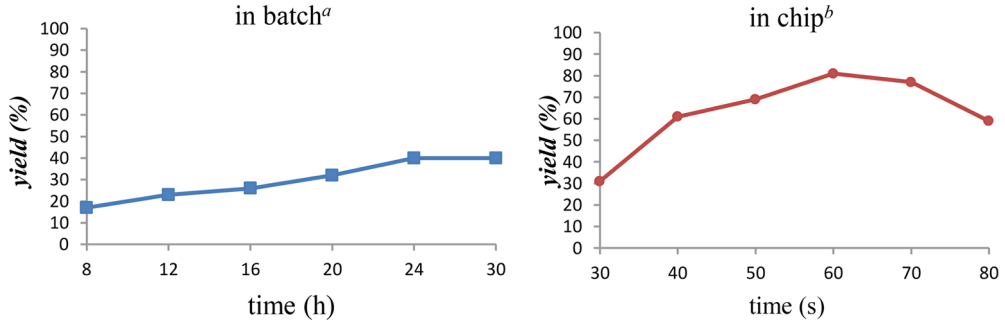



**Figure 1.** Comparison of yield in batch and chip. [a] Reaction conditions in batch: 1 mmol of **1a**, 0.2 mmol of KI, 6 mmol of **2** in 1 mL of $H_2O$, 40 °C. [b] Reaction conditions in chip: Solution A: 1 mmol **1a** in 6 mmol **2** (70% in $H_2O$), pumping the organic phase in syringe A (Titration of TBHP in the aqueous phase was only 0.062 mmol, which could be ignored); Solution B: 0.2 mmol KI in 1 mL of $H_2O$; flow rate of syringe A = flow rate of syringe B (μL/min); the volume of chip reactor = 10 μL.



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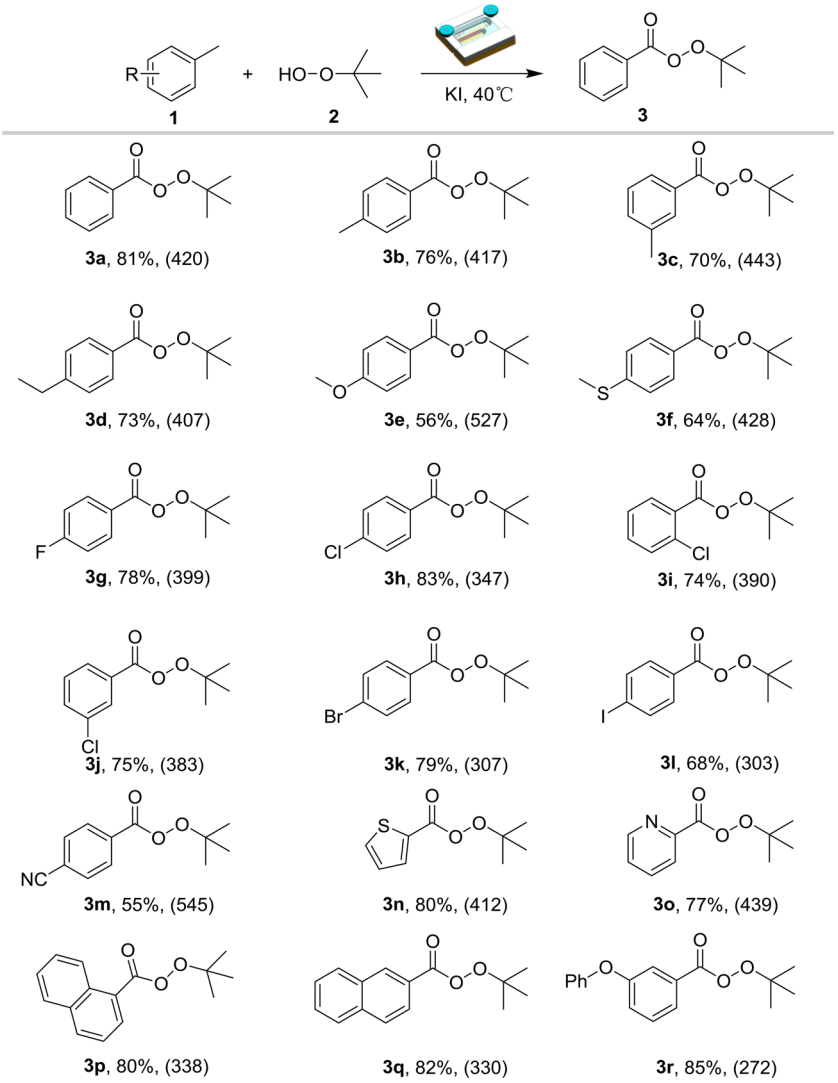
**Table 2. Substrate Scope of Toluene Derivatives**[a,b,c]



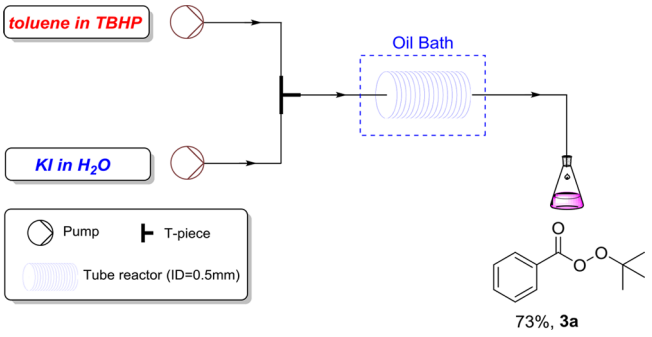

[a]Reaction conditions: Solution A: 1 mmol **1** in 6 mmol of **2** (70% in $H_2O$), pumping the organic phase in syringe A; Solution B: 0.2 mmol of KI in 1 mL of $H_2O$; flow rate$_a$ = flow rate$_b$ = 5 $\mu$L/min; the volume of chip reactor = 10 $\mu$L. [b]Isolated yield. [c]Process mass intensity (PMI) = (total mass in a process or process step)/(mass of product).

results were summarized in Table 2. Generally, toluene derivatives **1** with different substitution patterns (electron-withdrawing or -donating groups) proceeded smoothly with TBHP **2**. In particular, a series of substituents, such as alkyl, sulfide, halide, and cyano groups at the *para*-, *meta*-, and *ortho*-position, provided the corresponding products in 55% to 83% yields (Table 2, **3b**−**3m**). Notably, heteroarenes including 2-methylthiophene and 2-methylthiophene were also suitable for our method (Table 2, **3n**−**3o**). Moreover, 1-methylnaphthalene and 2-methylnaphthalene were tolerated under the optimized conditions and afforded the desired products **3p** and **3q** in 80% and 82% yield, respectively.

To explore the practical value of this method, a scale-up continuous flow reactor was set up, which is composed of two syringe pumps, a T-piece micromixer, and a tube reactor (Scheme 2). The reaction proceeded effectively in this continuous flow reactor system, and product **3a** was successfully obtained in good yield.

Next, the mechanism of the method was investigated by some control experiments (Scheme 3). The target product **3a** was successfully obtained from benzyl alcohol **A** and benzaldehyde **B** under the optimized conditions, respectively

**Scheme 2. A Scale-up Continuous Flow Reactor**[a]




[a]Reaction conditions: Solution A: 10 mmol **1** in 60 mmol **2** (70% in $H_2O$), pumping the organic phase in syringe A; Solution B: 2 mmol KI in 15 mL $H_2O$; flow rate$_a$ = flow rate$_b$ = 0.5 mL/min; the volume of tube reactor = 10 mL; T = 40 °C.



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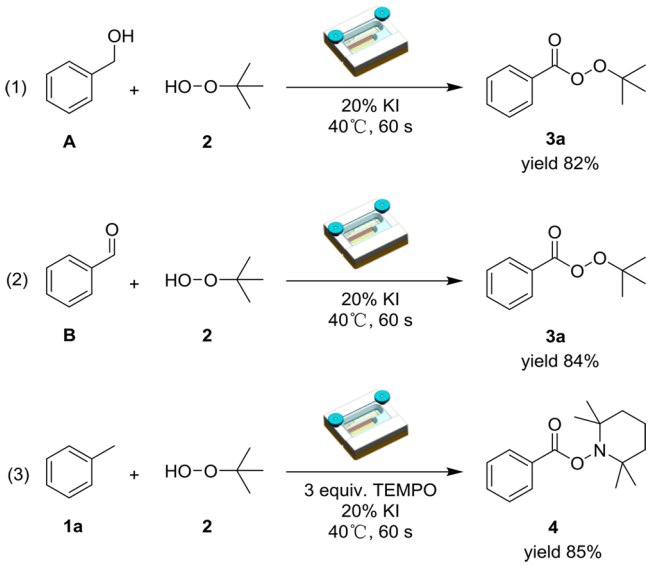
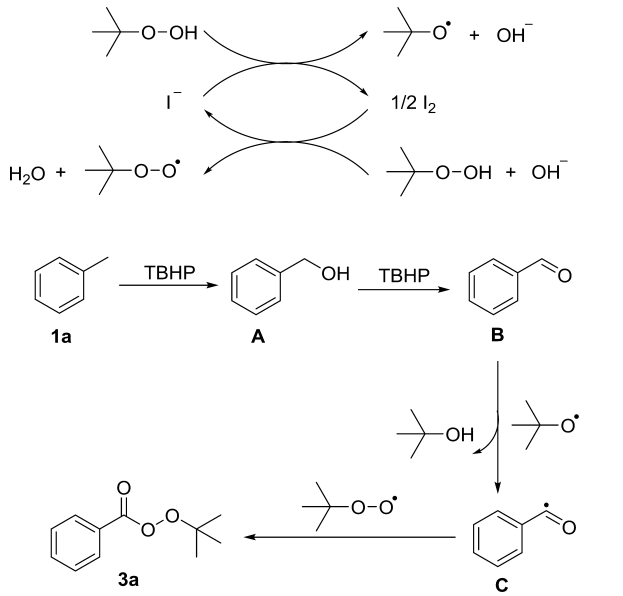
**Scheme 3. Experiments on the Study of Mechanism**




(Scheme 3, eqs 1 and 2). Product **3a** was formed at trace level in the presence of a radical inhibitor (TEMPO), and compound **4** was obtained in 85% yield (Scheme 3, eq 3). It clearly demonstrated that an acyl radical is formed in this reaction process.

On the basis of the above-mentioned results and previous reports,[3,11] a plausible mechanism for the synthesis of *tert*-butyl peresters was proposed as shown in Scheme 4. First, toluene **1a**

**Scheme 4. Plausible Reaction Mechanism**




is transformed to benzyl alcohol **A**,[11e] which is further oxidized into benzaldehyde **B** in the presence TBHP. Afterward, acyl radical **C** was formed via the cleavage of the aldehydic C–H bond in the presence of *tert*-butoxyl, which was generated in the TBHP-KI catalytic cycle. Finally, the acyl radical **C** couples with a *tert*-butylperoxy radical to afford the desired product **3a**.

## CONCLUSION

In summary, we have developed a green and efficient KI-catalyzed organic–aqueous two-phase reaction route to *tert*-butyl peresters from methyl arenes in a microfluidic chip reactor, which not only improved the yield drastically but also overcame the poor mixing efficiency of the organic–aqueous two-phase reaction in batch. Moreover, a series of peresters were obtained in moderate to good yields from commercially available methyl arenes and TBHP. A scale-up continuous flow system was successfully applied to this method, which verified its great practical application in synthetic chemistry. Further investigation on the craft enlargement experiment and application of this method are ongoing in our laboratory.

## EXPERIMENTAL SECTION

Methyl arenes **1** (1 mmol) was dissolved in TBHP **2** (6 mmol, 70% in $H_2O$), and the mixture was divided into an organic phase and an aqueous phase. Titration of TBHP in the aqueous phase revealed only 0.062 mmol, which could be ignored. Then the organic phase was pumped in syringe A. KI (0.2 mmol) was dissolved in 1 mL of $H_2O$, which was pumped in syringe B. The flow rates of syringe A and syringe B were 5 $\mu$L/min, and the volume of chip reactor was 10 $\mu$L. The temperature of the chip was set at 40 °C. The outflow of the reaction mixture was collected, then quenched with saturated $Na_2S_2O_3$ solution (10 mL), and extracted with ethyl acetate (30 mL × 2). The organic layer was dried over anhydrous sodium sulfate, and solvent was removed under vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum, affording the desired product **3** in good yields.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.7b00248.

Microfluidic chip reactor device, the scale-up continuous flow system, experimental procedures and full characterization of all compounds, spectral data, and $^1$H and $^{13}$C NMR spectra for all products (PDF)

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### Notes

The authors declare no competing financial interest.

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