FULL PAPER

Synthesis of arenediazonium salts and Suzuki- Miyaura cross-coupling reaction in microreactors

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Abstract

The process characteristics of two main steps in the preparation of 4-nitrobiphenyl (4-NBP) from 4-nitroaniline (PNA) were clearly revealed by applying two continuous-flow microreactors. The first step was the synthesis of 4-nitrobenzene diazonium tetrafluoroborate (4-NBDT) through the diazotization reaction. The reaction temperature, the residence time, and the molar ratio of different reactants were investigated to achieve optimal reaction conditions with the highest yield of 4-NBDT. Notably, the yield of 4-NBDT reached 97% at 25 °C only in 2.3 s with the optimal molar ratio of HBF_4, $NaNO_2$ and PNA (i.e., 2.72:1.05:1). The second step was the Suzuki-Miyaura cross-coupling reaction, in which HNO_3 was used to transform the reaction system into a homogeneous state. The effects of mixing performance, the molar percentage of $Pd(OAc)_2$ to 4-NBDT, the reaction temperature and the residence time on the Suzuki-Miyaura cross-coupling reaction were investigated systematically. With the molar percentage of $Pd(OAc)_2$ to 4-NBDT of 1 mol%, the yield of 4-nitrobiphenyl (4-NBP) was optimized to 99% in just 13 min at 25 °C. This study demonstrated the excellent potential of utilizing the continuous-flow microreactor for the diazotization and the following Suzuki-Miyaura cross-coupling reaction.

Keywords Diazotization · Suzuki-Miyaura cross-coupling · Continuous-flow synthesis · Microreactor · 4-nitrobiphenyl

Introduction

As a powerful tool for synthesizing unsymmetrical biaryls, the Suzuki-Miyaura cross-coupling reaction (Scheme 1) was widely used to synthesize liquid crystal materials, dyes, and drugs. [1–3] Since the pioneering work from Suzuki and Miyaura, the reported Suzuki-Miyaura cross-coupling reaction processes have widely used heterogeneous sources of palladium (Pd) immobilized in nanoparticles or packed bed. [4–7] However, despite the immobilization of palladium, there is strong proof that the catalytically active species is actually leached into the reaction stream as a homogeneous Pd catalyst. [8] The general mechanism of the Suzuki-Miyaura cross-coupling reaction includes a catalytic cycle of oxidative addition, transmetalation and reductive elimination. [4] In a typical heterogeneous catalysis process, the leached Pd(II) is considered to be responsible for the catalysis with a (quasi)homogeneous mechanism. [9, 10] Besides, as the inactive palladium black is easily formed due to the poor stability of catalysts, the extra ligand or high loading of catalysts is needed to maintain the reaction efficiency. [11] Hence, by using a homogeneous source of palladium (such as $Pd(OAc)_2$ and Pd_2dba_3) accompanied with an appropriate ligand, the Suzuki-Miyaura cross-coupling reaction processes can be efficiently operated under mild conditions without mass transfer limitations in the liquid phase. [10]

Microreactors as efficient process intensification platforms have been widely applied for reaction processes, [12] such as oxidation, [13, 14] nitration, [15, 16] diazotization, [17, 18] owing to its large specific surface area, short transfer distance, high mixing efficiency, fast heat and mass transfer rates, and ensured process safety. Motivated by these advantages, many researchers have applied microreactor technology into
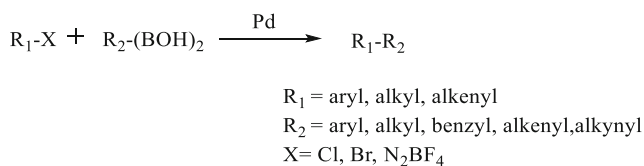
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$$R_1\text{-}X + R_2\text{-}(BOH)_2 \xrightarrow{\;Pd\;} R_1\text{-}R_2$$

R₁ = aryl, alkyl, alkenyl
R₂ = aryl, alkyl, benzyl, alkenyl, alkynyl
X = Cl, Br, N₂BF₄

Scheme 1 Suzuki-Miyaura cross-coupling reaction

homogeneous Suzuki-Miyaura cross-coupling reactions. [19, 20] Ionic liquid (IL) was used to transform the heterogeneous Suzuki-Miyaura cross-coupling reaction to a homogeneous state and implemented in a continuous-flow microreactor system. [21] Due to the better mixing performance of microreactor, the yield and selectivity were improved than the batch reactor. Next, a droplet-based microreactor was used in the IL-based Suzuki-Miyaura cross-coupling reaction to solve the clogging problem in the microchannel. The yield in droplet-based microreactor was improved 9.3% compared to the traditional batch reactor, but there was only a slight increasement compared to the single-phase microreactor. [22] Buchwald and Jensen also developed an automated droplet-flow microfluidic system for the optimization of Pd-catalyzed Suzuki-Miyaura cross-coupling reactions. [23] Integrated automation and online analytics can study Pd source, ligand, and continuous variables simultaneously, giving efficient optimization and understanding of the reaction process. The majority of the Suzuki-Miyaura cross-coupling reaction studies, as mentioned above, used halogenated electrophiles.

In recent years, arenediazonium salts have attracted significant attention as aryl electrophilic components because they can be easily produced from corresponding aromatic amines with high yield and are more reactive than halogenated hydrocarbons. [24, 25] Its application in cross-coupling reactions has been extensively studied by researchers. [26–29] The reaction of aniline with HNO_2 to synthesize the arenediazonium salts is called diazotization. [12] As the aromatic amine diazotization process was exothermic and rapid, it should be conducted at low temperatures in a batch reactor to decrease the safety risk. [30, 31] Simultaneously, the thermal instability of the diazonium intermediate and the uncontrollable thermal decomposition of arendiazonium salts increased the requirements of the reactors heat transfer capacity. Organ et al. [32] reported a three-step continuous-flow system (diazotization, iododediazotization and Suzuki-Miyaura cross-coupling reaction) constructed by three pieces of PFA capillary tubing (ID = 1.52 mm) with different volumes. Biphenyl compounds were continuously produced from aniline derivatives with satisfactory yields at 60 °C and the total reaction time was about one hour. Except this study combining the diazotization with the Suzuki-Miyaura cross-coupling reaction in microreactors, more studies about diazotization in microreactors were used for the other two- or multi-step reactions, such as Heck-Matsuda reaction, [33, 34] Balz-Schiemann reaction, [17,

31] Sandmeyer reaction, [35] Meerwein arylation, [36] and diazo coupling reaction. [37] Although diazonium salts are hazardous, continuous-flow processing has the benefit of making such compounds in situ and immediately consuming them. [30, 38, 39] Few studies did evaluate the diazotization process alone due to the instability of diazonium intermediates. Most of studies only have characterized the diazotization efficiency by the yield in the final step, let alone the effects of operational conditions on the yields of arenediazonium salts were systematically investigated in microreactors. Besides, all reported studies [40–42] about the Suzuki-Miyaura cross-coupling reaction using arenediazonium salts as reactants were carried out in batch reactors to our best of knowledge. Moreover, further process optimization of the Suzuki-Miyaura cross-coupling reaction should be investigated to increase the reaction selectivity and the yield of target products, such as the stability and the dosage of the catalysts, the residence time and the reaction temperature.

In this work, 4-nitrobiphenyl (4-NBP) was synthesized from 4-nitroaniline (PNA) in two steps, as shown in Scheme 2. Step 1 was the diazotization of PNA to 4-nitrobenzene diazonium tetrafluoroborate (4-NBDT), while Step 2 was the Suzuki-Miyaura cross-coupling reaction. These two steps were conducted in two continuous-flow microreactors separately in order to clearly reveal their process characteristics. It should be noted that 4-NBDT is much more stable compared with halogenated diazonium salts, and thus the diazotization (Step 1) can be studied in terms of the 4-NBDT yield. In the diazotization process, acetonitrile (MeCN) was selected as the solvent to avoid the precipitation of diazonium salts in the microreactor. The diazotization temperature, the residence time, and the molar ratio of HBF_4 and $NaNO_2$ to PNA were optimized to obtain a high yield of 4-NBDT. In the Suzuki-Miyaura cross-coupling reaction process, HNO_3 was used to promote the dissolution of $Pd(OAc)_2$, maintaining the reaction system in a homogeneous state. Also, effects of the molar percentage of $Pd(OAc)_2$ to 4-NBDT, the reaction temperature and the residence time on the yields of 4-NBP and other homocoupling by-products were investigated systematically.
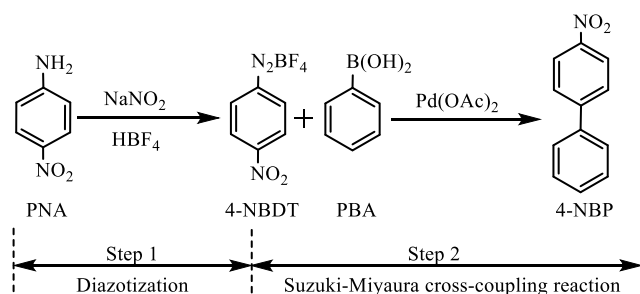
Scheme 2 Synthesis of 4-nitrobiphenyl (4-NBP) from 4-nitroaniline (PNA)

Experimental section

Materials

Hexadeuteriodimethyl sulfoxide (DMSO-d$_6$, AR, 99.0 wt%), 1,3,5-trioxane (AR, 99.0 wt%), 4-nitroaniline (PNA) (AR, 99.0 wt%) and 4-nitrobenzene diazonium tetrafluoroborate (4-NBDT, AR, 97.0 wt%) were purchased from Macklin Biochemical Co., Ltd. (Shanghai, China). Fluoroboric acid (HBF$_4$, AR, 40.0 wt%), phenylboronic acid (PBA, AR, 98.0 wt%), sodium nitrite (NaNO$_2$, AR, 99.0 wt%), and nitric acid (HNO$_3$, AR, 65.0 wt%) were purchased from Meyer Biochemical Co., Ltd. (Shanghai, China). Biphenyl (AR, 98.0 wt%), 4,4′-dinitrobiphenyl (AR, 99.0 wt%) and 4-nitrobiphenyl (4-NBP, AR, 97.0 wt%) were purchased from Aladdin Biochemical Co., Ltd. (Shanghai, China). Pd(OAc)$_2$ (AR, 99.0 wt%) was purchased from Energy Chemical Co., Ltd. (Shanghai, China). Acetonitrile (MeCN, 99.9%, HPLC), and methanol (MeOH, 99.9%, HPLC) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). All the chemical reagents mentioned above were used directly in the experiments without further purification.

Synthesis of 4-NBDT and 4-NBP

The schematic overview of the capillary microreactor system is shown in Fig. 1. Twosteps, namely the diazotization and the Suzuki-Miyaura cross-coupling reaction, were operated separately in this work. In the diazotization step synthesizing 4-NBDT, Solution A was prepared by dissolving PNA and HBF$_4$ in MeCN with the fixed PNA concentration of 0.81 mol/L, while Solution B consisted of NaNO$_2$, s-trioxane (internal standard, 0.08 mol/L) and water. The volumetric flow rate ratio of Solution A to Solution B was fixed at 1. Solution A and B were delivered into the capillary microreactor system by two syringe pumps (NE-1200, New Era Pump System, Inc., United States). Both these two solutions were preheated to the set temperature in coiled capillaries before they mixed in a polyetheretherketone (PEEK) micromixer. The residence time for the diazotization could

be easily controlled by varying the perfluoroalkoxy (PFA) capillary length. The whole capillary microreactor system, which consisted of the T-micromixer and capillaries with the same inner diameter (ID = 1.0 mm), was submerged in a water bath maintaining the set temperature (25–65 °C). At the capillary microreactor outlet, the reaction was quenched in a collection vessel containing a suitable amount of urea by consuming the residual NaNO$_2$. The liquid sample was collected for the further determination of the 4-NBDT yield. The yield of 4-NBDT was calculated from PNA. T_D and t_D represent the reaction temperature and the residence time for the diazotization, respectively.

In the Suzuki-Miyaura cross-coupling reaction step, the reactant 4-NBDT was crystallized and purified from the diazotization step with a purity of 99%. The whole capillary microreactor system setup in this step was the same as in the diazotization, as shown in Fig. 1. Solution C was prepared by dissolving phenylboronic acid (PBA) (0.101 mol/L) in MeOH, while 4-NBDT (0.0169 mol/L) and Pd(OAc)$_2$ were dissolved in MeOH as Solution D. The volumetric flow rate ratio of Solution D to Solution C was fixed at 5. The Suzuki-Miyaura cross-coupling reaction was quenched by diluting the liquid effluent from the capillary microreactor system in a collection vessel containing a known volume of MeCN. The yields of all the products were calculated from 4-NBDT. T_S and t_S represent the reaction temperature and residence time for the Suzuki-Miyaura cross-coupling reaction, respectively.

Analysis

The yield of 4-NBDT was determined by ^{1}HNMR spectra recorded on a Bruker 400 MHz spectrometer with DMSO-d$_6$ as the solvent, while s-trioxane was used as an internal standard. [43] A high-performance liquid chromatography (HPLC, Shimadzu LC -16, Japan) equipped with a C18 column (WondaSil C18-WR 5 μm, 4.6 × 150 mm) was used for determining the yields of 4-NBP, biphenyl, 4,4′-dinitrobiphenyl and the conversion of 4-NBDT. The mobile phase was a mixture of ultrapure water (0.1 wt% formic acid) and MeCN with a flow
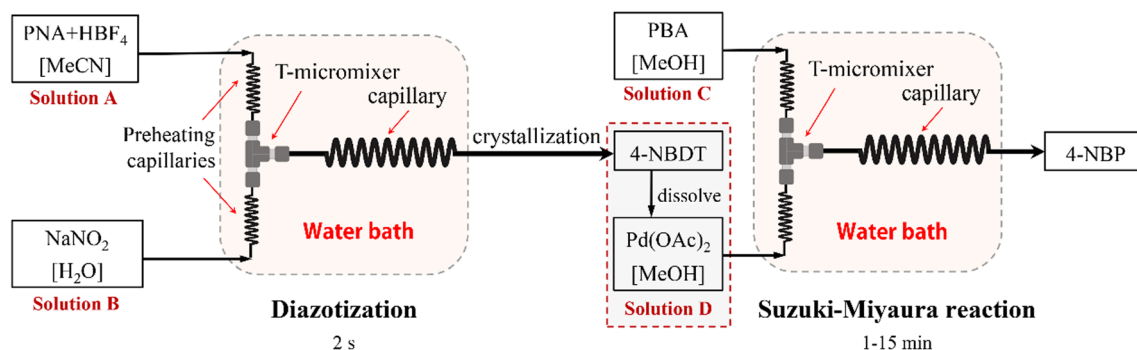

Fig. 1 Schematic overview of the experimental setup for the diazotization and the Suzuki-Miyaura cross-coupling reaction

rate of 0.8 mL/min (the ratio was 65:35). The detection wavelength of the UV-detector was set at 259 and 304 nm.

Results and discussion

Diazotization in the capillary microreactor

The diazotization reaction performance

The total volumetric flow rate must be determined to ensure an efficient mixing performance when operating such a fast diazotization reaction in a microreactor system. Figure 2 shows the effect of the total volumetric flow rate on the yield of 4-NBDT at the same residence time. The mixing performance of two feed solutions was improved in the T-micromixer and the following capillary when the total volumetric flow rate increased. [44] As shown in Fig. 2, the yield of 4-NBDT was basically the same for various volumetric flow rates from 2 to 15 mL/min, indicating that the mixing performance was not a limiting factor for the diazotization performance under the involved experimental conditions. That is, the mixing was excellent and fast enough for the diazotization. All the following experiments were operated with a total volumetric flow rate of 2 mL/min ($Q_A = Q_B = 1$ mL/min) for the continuous-flow diazotization process.
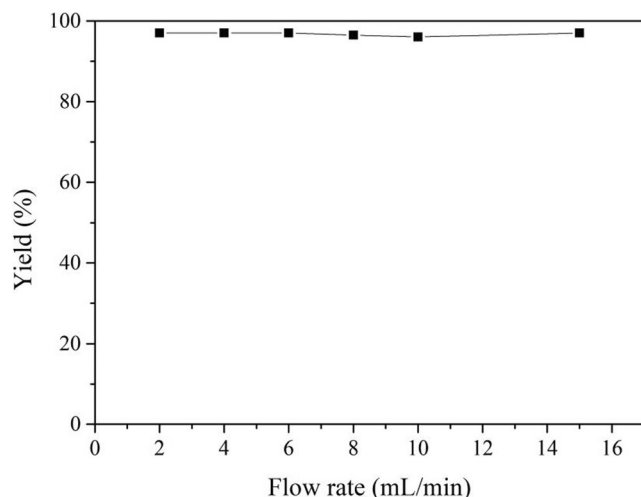
Effect of the molar ratio of HBF$_4$ and NaNO$_2$ to PNA on the diazotization performance

In general, the diazotization is carried out under highly acidic conditions and HNO$_2$ acts as a diazo reagent which is in-situ synthesized by the reaction of mineral acid and NaNO$_2$. According to previous literature reports, [45, 46] the diazotization was the first order to the aniline substrate and the second-order to nitrous acid, indicating the importance of the acid concentration to the diazotization reaction rate. Typically, more than two equivalents of mineral acid were needed based on the stoichiometry of the diazotization to accelerate the formation of diazonium salts. Besides, low nitrous acid concentration results in the reduction of the diazonium salt stability as unreacted aromatic amines can react with diazonium salts to form by-products (e.g., azo compounds). [46] A stoichiometric or a slightly larger amount of NaNO$_2$ is often used in the diazotization process to prevent an excess of the nitrous acid formation. Therefore, the effects of HBF$_4$ and NaNO$_2$ dosages on the diazotization process should be investigated in detail.

Figure 3 shows the effect of the molar ratio of HBF$_4$ to PNA on the yield of 4-NBDT in the capillary microreactor system while maintaining the same residence time ($t_D = 2.3$ s) and the same reaction temperature ($T_D = 25$ °C). The molar ratio of HBF$_4$ to PNA was varied by changing the concentration of HBF$_4$ with a constant PNA concentration. The yield of 4-NBDT increased with the increase of the molar ratio of HBF$_4$ to PNA. The highest yield of 4-NBDT reached 98.5% with the molar ratio of HBF$_4$ to PNA being 3.11. However, the promotion on the yield of 4-NBDT was less significant with the further increase of the molar ratio of HBF$_4$ to PNA after its value reached 2.72.

As shown in Fig. 4, the effect of the molar ratio of NaNO$_2$ to PNA on the yield of 4-NBDT was investigated in the capillary microreactor system with three different molar ratios of HBF$_4$ to PNA. The yield of 4-NBDT firstly increased and then decreased with the increase in the molar ratio of NaNO$_2$ to PNA from 1.0 to 1.4. The highest yield of 4-NBDT could reach 98% with the molar ratio of NaNO$_2$ to PNA being 1.05. However, 4-NBDT was found to precipitate at the molar
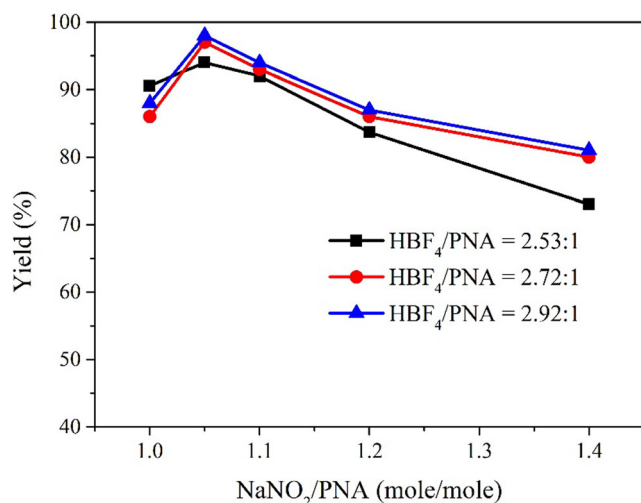

Fig. 2 Effect of total volumetric flow rate on the yield of 4-NBDT in the capillary microreactor at the same residence time (the molar ratio of HBF$_4$, NaNO$_2$ and PNA was 2.72:1.05:1, $T_D = 25$ °C, and $t_D = 2.3$ s)
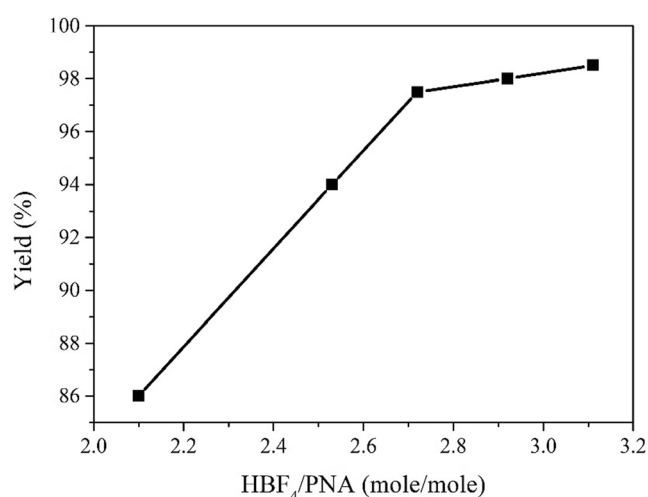
Fig. 3 Effect of the molar ratio of HBF$_4$ to PNA on the yield of 4-NBDT in the capillary microreactor (the molar ratio of NaNO$_2$ to PNA was 1.05, $T_D = 25$ °C, and $t_D = 2.3$ s)

Fig. 4 Effect of the molar ratio of $NaNO_2$ to PNA on the yield of 4-NBDT in the capillary microreactor with three different molar ratios of HBF_4 to PNA ($T_D = 25$ °C, and $t_D = 2.3$ s)

Fig. 5 Effects of reaction temperature and residence time on the yield of 4-NBDT in the capillary microreactor with a constant molar ratio of HBF_4, $NaNO_2$ and PNA (2.72:1.05:1)

ratio of HBF_4 to PNA of 2.92, leading to a blockage of the capillary microreactor after a period of running time. More water from the HBF_4 solution was introduced into the microreactor system with increasing the concentration of HBF_4, leading to a decrease of the 4-NBDT solubility in the MeCN and water mixed solution. The molar ratio of HBF_4 to PNA of 2.72 was selected without the microreactor blockage. As mentioned above, the diazotization was considered to be the second-order to the nitrous acid, and the concentration of nitrous acid increased with the increase of the $NaNO_2$ concentration leading to a higher reaction rate and a higher yield of 4-NBDT. However, the yield of 4-NBDT was decreased sharply to 73% with the further increase of the molar ratio of $NaNO_2$ to PNA from 1.05 to 1.4. Because the decomposition of diazonium salts can quickly happen with a significant excess of $NaNO_2$. [30] Hence, the optimal molar ratio of HBF_4, $NaNO_2$ and PNA was determined as 2.72:1.05:1, with the yield of 4-NBDT reaching 97%.

Effects of reaction temperature and residence time on the diazotization performance

The reaction temperature plays an essential role on the reaction process, especially for rapid and exothermic reactions like diazotization. As a typical diazotization process in a batch reactor, the reaction temperature is often controlled below 0 °C to operate the diazotization with a relatively low reaction rate for preventing the temperature runaway. Due to the efficient heat transfer performance of the microreactor, the diazotization process can be conducted under higher reaction temperatures. The diazonium salts are unstable if the reaction temperature reaches a certain value, and thus the reaction temperature and the residence time should be optimized. Fig. 5 shows the effects of the reaction temperature and the residence
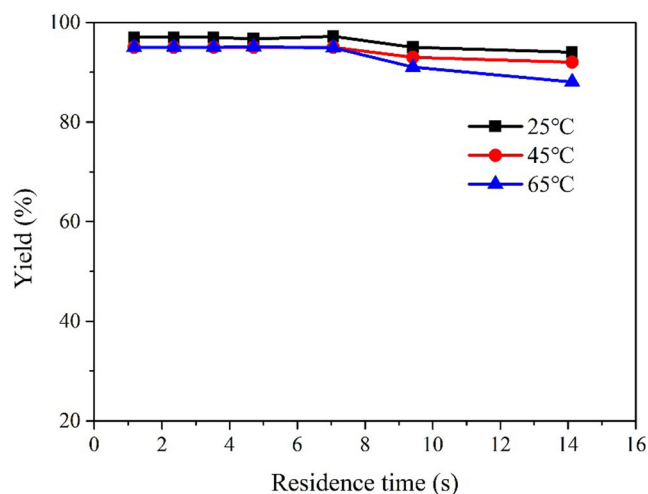
time on the yield of 4-NBDT in the capillary microreactor system with a constant molar ratio of HBF_4, $NaNO_2$ and PNA (i.e., 2.72:1.05:1). The yield of 4-NBDT reached 97% in just 2.3 s at 25 °C and then decreased slightly with further increasing the residence time due to the decomposition of the diazonium salts that could be proved by the existence of by-products. [17] When the residence time was shorter than 4 s, the yield of 4-NBDT slightly decreased from 97% to 95% with the increase of the reaction temperature from 25 °C to 65 °C. However, the impact of the reaction temperature on the yield of 4-NBDT was more sensitive than the residence time. A higher reaction temperature boosted the decomposition of the diazonium salts leading to an inevitable decrease of the 4-NBDT yield. These results indicated that the decrease of the reaction temperature and a suitable residence time were beneficial for improving the yield of 4-NBDT. We also operated the diazotization reaction at a temperature less than 25 °C, resulting in the blockage of the capillary microreactor by the precipitated diazonium salts, which only could be prevented by the decrease in the concentration of reactants. Hence, to operate the diazotization in a capillary microreactor at a mild temperature with high reaction efficiency and appropriate energy consumption, the reaction temperature of 25 °C and the residence time of 2.3 s were considered as optimal operational conditions.

The transport properties provided by batch reactors cannot match the reaction kinetics of such a fast reaction, leading to uneven local temperature and concentration distribution which is not conducive to the diazotization performance. These results indicated the importance of precisely controlling the molar ratio of reactants, the reaction temperature and the residence time of the diazotization process and highlighted the microreactor with remarkable

transport efficiency for achieving a high yield of the target product (4-NBDT).

Suzuki-Miyaura cross-coupling reaction in the capillary microreactor system

Continuous-flow operation with a homogeneous reaction system

In a typical batch operation using arenediazonium salts as reactants, the reactant and the catalyst are added into the reactor as solids in the absence of base. [41, 47] For operating the Suzuki-Miyaura cross-coupling reaction under the homogeneous state in a continuous-flow microreactor system, all the reagents need to be dissolved into solvents in advance. According to the literature results, [48] MeOH is often selected as a more suitable solvent for the Suzuki-Miyaura cross-coupling reaction compared with MeCN, EtOH, DMF, DMSO, THF and other solvents. In addition to the use of MeOH, a moderate amount of HNO_3 was added into MeOH in order to further increase the solubility of $Pd(OAc)_2$, transforming the reaction system into a homogeneous system.

For the first time conducting the Suzuki-Miyaura cross-coupling reaction under acidic conditions, the effect of the acid addition on the reaction performance should be investigated. Figure 6 shows the effect of the HNO_3 concentration on the yield of 4-NBP in the capillary microreactor system with a fixed molar percentage (1 mol%) of $Pd(OAc)_2$ to 4-NBDT at 25 °C. The homogeneous Suzuki-Miyaura cross-coupling reaction was successfully carried out in the capillary microreactor system under acidic conditions. The yield of 4-NBP decreased from 75% to 40% with increasing the concentration of HNO_3 from 11.5 mmol/L to 60 mmol/L (pH = 1 ~ 2). It was deduced that the reaction rate was reduced by the
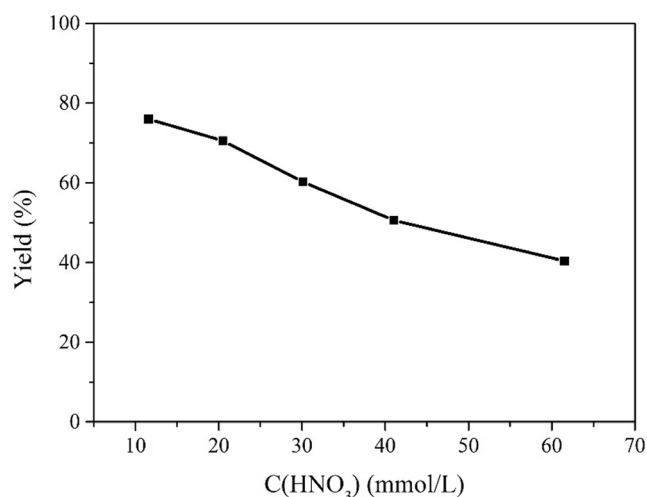
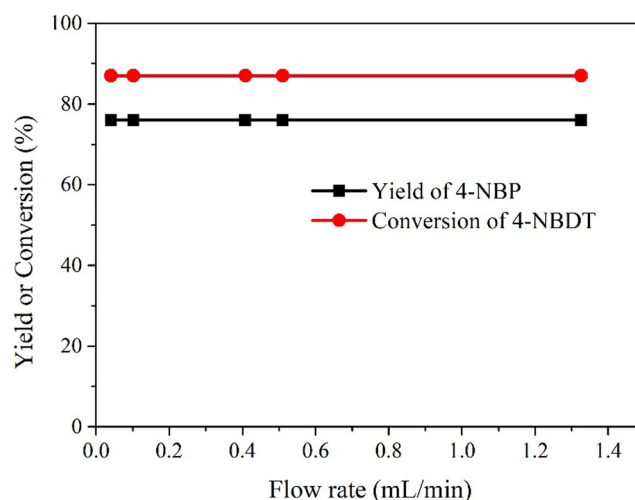strong acid and water in the acid solution. By far, we are still investigating the effect of the acidic condition on the Suzuki-Miyaura cross-coupling reaction performance, and more detailed experimental results will be concluded in our future work. Based on the present experimental results, the HNO_3 concentration of 11.5 mmol/L could be an optimal value for the continuous-flow homogeneous Suzuki-Miyaura cross-coupling reaction process.

The Suzuki-Miyaura cross-coupling reaction performance

The total volumetric flow rate of reactant solutions should be determined to ensure efficient mixing performance in the capillary microreactor system. Figure 7 shows the variation of the 4-NBP yield with different total volumetric flow rates at the same residence time. The volumetric flow rate ratio of Solution D to Solution C was maintained at 5. As mentioned above, the mixing performance between two solutions became better in the microreactor with the increasing the volumetric flow rate. The yield of 4-NBP was basically the same in the range of chosen flow conditions, indicating that the mixing performance was not the limiting factor for the Suzuki-Miyaura cross-coupling reaction process in our experiments. All the following experiments were operated with a total volumetric flow rate of 0.3 mL/min (Q_C = 0.05 mL/min and Q_D = 0.25 mL/min) for the continuous-flow Suzuki-Miyaura cross-coupling reaction process.

In previous studies, halogenated hydrocarbons were often used as reactants in the Suzuki-Miyaura cross-coupling reaction at a relatively high temperature, and the reactions could be quenched effectively by decreasing the reaction temperature or separating the catalysts from the products in the heterogeneous process. However, for the Suzuki-Miyaura cross-coupling reaction with the use

Fig. 6 Effect of the concentration of HNO_3 on the yield of 4-NBP in the capillary microreactor system (Q_C = 0.05 mL/min, Q_D = 0.25 mL/min, t_S = 7.85 min, T_S = 25 °C, and $Pd(OAc)_2$ = 1 mol%)
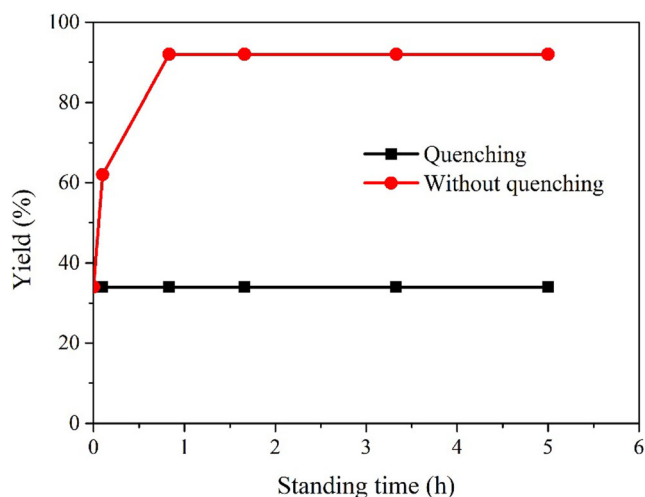

Fig. 7 Effect of the total volumetric flow rate on the yield of 4-NBP and the conversion of 4-NBDT in the capillary microreactor at the same residence time (t_S = 7.7 min, T_S = 25 °C, $Pd(OAc)_2$ = 1 mol%, and $C(HNO_3)$ = 11.5 mmol/L)

of a diazonium salt as a reactant, which was operated at mild reaction temperature, the low-temperature quenching method was infeasible as the reaction would progress in the analysis units. An efficient quenching method should be developed for accurate determination of the reaction performance. In the continuous-flow homogeneous operation at room temperature, MeCN was chosen as the quencher. To illustrate the efficiency of the quenching operation, we collected the reaction solution at the outlet of the capillary microreactor with or without quenching and then left the solution for a period of standing time before analysis. Figure 8 shows the effect of quenching on the yield of 4-NBP at different standing times. The yield of 4-NBP still increased in one hour without quenching, while the yield remained at a certain level with quenching. Hence, MeCN was proved to be an efficient quencher in the continuous-flow homogeneous Suzuki-Miyaura cross-coupling reaction.
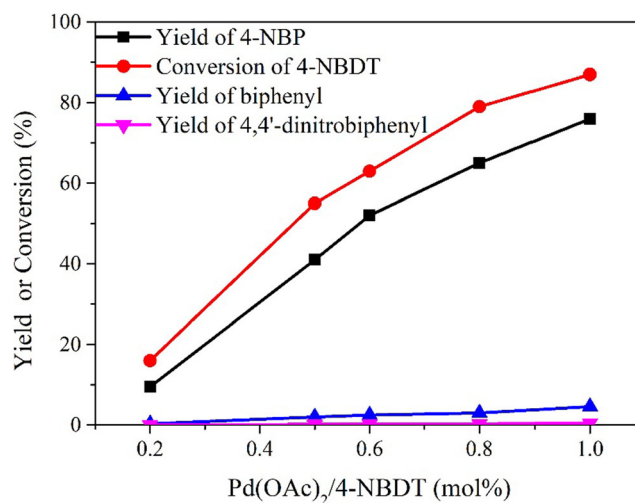
Effect of Pd(OAc)$_2$ on the Suzuki-Miyaura cross-coupling reaction performance

The amount of the catalyst plays a vital role in the Suzuki-Miyaura cross-coupling reaction. Pd(OAc)$_2$ was selected as a catalyst without the use of any ligands in this work due to its low cost and high reaction activity. Figure 9 shows the effect of the molar percentage of Pd(OAc)$_2$ to 4-NBDT on the yields of 4-NBP and by-products (biphenyl and 4,4'-dinitrobiphenyl) and the conversion of 4-NBDT at the residence time of 7.85 min and 25 °C.

With the molar percentage of Pd(OAc)$_2$ to 4-NBDT increasing from 0.2 mol% to 1 mol%, the conversion of 4-NBDT and the yield of 4-NBP increased from 15% to 87% and 10% to
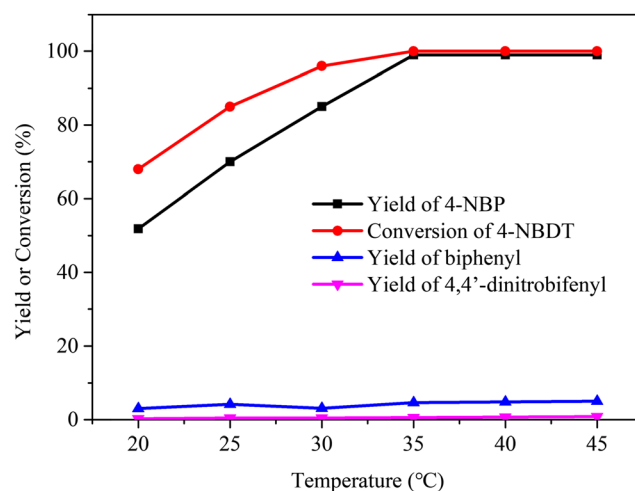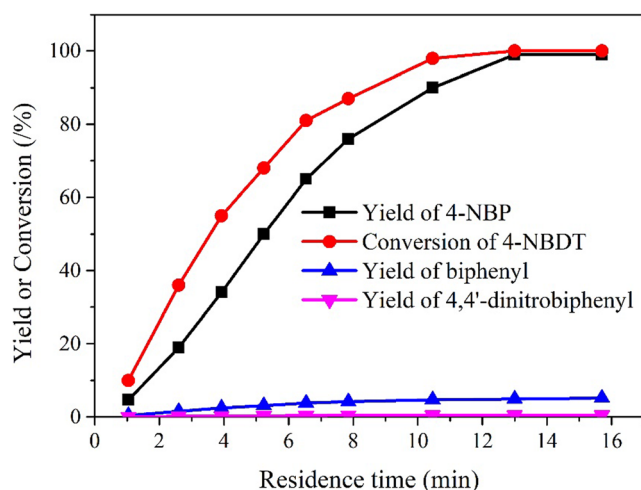

Fig. 9 Effect of the molar percentage of Pd(OAc)$_2$ to 4-NBDT on the Suzuki-Miyaura cross-coupling reaction performance in the capillary microreactor ($t_S = 7.85$ min, $T_S = 25$ °C, and $C(HNO_3) = 11.5$ mmol/L)

75%, respectively. Two main by-products, including biphenyl and 4,4'-dinitrobiphenyl, were detected in this work. [49, 50] The homocoupling of PBA was promoted by increasing the molar percentage of Pd(OAc)$_2$ to 4-NBDT, while the yield of biphenyl increased from 0.5% to 4.6%. Whereas, the biphenyl formation decreases the PBA concentration, a suitable excess of PBA is often used in the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction. As can be shown in Fig. 9, the generation of 4,4'-dinitrobiphenyl from the homocoupling of 4-NBDT was less sensitive to the molar percentage of Pd(OAc)$_2$ to 4-NBDT. To achieve the highest yield of the 4-NBP and the reaction selectivity, 1 mol% Pd(OAc)$_2$ was considered as an optimal value for this continuous-flow Suzuki-Miyaura cross-coupling reaction.

Fig. 8 Effect of MeCN on the yield of 4-NBP in the capillary microreactor ($t_S = 3.92$ min, $T_S = 25$ °C, Pd(OAc)$_2 = 1$ mol%, and $C(HNO_3) = 11.5$ mmol/L)

Fig. 10 Effect of the temperature on the Suzuki-Miyaura cross-coupling reaction performance in the capillary microreactor system ($t_S = 7.85$ min, Pd(OAc)$_2 = 1$ mol%, and $C(HNO_3) = 11.5$ mmol/L)

Fig. 11 Effect of the residence time on the Suzuki-Miyaura cross-coupling reaction performance in the capillary microreactor system (T_S = 25 °C, Pd(OAc)$_2$ = 1 mol%, C(HNO$_3$) = 11.5 mmol/L)

Effects of reaction temperature and residence time on the Suzuki-Miyaura cross-coupling reaction performance

As is well known, intrinsic reaction rate constants usually increase with the temperature increase according to the Arrhenius Equation. We studied the effect of reaction temperature on the yields of 4-NBP and by-products (biphenyl and 4,4'-dinitrobiphenyl) and the conversion of 4-NBDT in the capillary microreactor system with the residence time of 7.85 min. As shown in Fig. 10, the yield of 4-NBP increased from 52% to 99% with the increase of the reaction temperature from 20 °C to 45 °C, while the conversion of 4-NBDT increased from 68% to 100%. These results indicated that the increase of the reaction temperature was beneficial for improving the reaction rate leading to a significant increase of the 4-NBP yield. Moreover, the effect of the reaction temperature on the yields of 4,4'-dinitrobiphenyl and biphenyl was not evident, while the yields of these two homocoupling by-products were maintained as 0.83% and 5%, respectively. It is worth noting that gas bubbles were gradually generated in the capillary microreactor when the reaction temperature was higher than 30 °C. To rule out the possibility of the MeOH

gasification and the 4-NBDT decomposition, we only pumped the MeOH solution (with or without 4-NBDT) into the capillary microreactor system under all the experimental conditions. No gas bubbles were observed in the capillary microreactor. According to the reaction mechanism, the gas bubbles were mainly formed by nitrogen (N$_2$) and produced due to the Suzuki-Miyaura cross-coupling reaction. Besides, the solubility of N$_2$ in MeOH decreased with the temperature rising, increasing the volumetric flow rate of N$_2$. The actual residence time of reactants at 40 °C with the existence of gas bubbles was immensely shortened compared to the residence time at 25 °C without the gas generation. Even so, the yield of 4-NBP and the conversion of 4-NBDT still reached the maximum value at 40 °C with the residence time less than 8 min. Hence, the increase of the reaction temperature was proved to accelerate the Suzuki-Miyaura cross-coupling reaction with a high reaction selectivity (99%).

The reaction rate was quite fast at high reaction temperatures, and a great deal of gas was generated in the capillary microreactor as the reaction progressed, which increased the difficulty to precisely control the residence time. In this work, we preferred to operate the Suzuki-Miyaura cross-coupling reaction at room temperature (25 °C) without N$_2$ releasing from the reaction system. Figure 11 shows the effect of the residence time on the yields of 4-NBP and by-products (biphenyl and 4,4'-dinitrobiphenyl) and the conversion of 4-NBDT in the capillary microreactor system at 25 °C. The residence time was varied by changing the length of the capillary microreactor with a constant volumetric flow rate of two reactant solutions (Q_C = 0.05 mL/min, and Q_D = 0.25 mL/min). The yield of 4-NBP increased significantly from 5% to 99% with the residence time varied from 1 min to 13 min, while the conversion of 4-NBDT increased from 10% to 100%. The yield of biphenyl increased from 0.38% to 5%, and the yield of 4,4'-dinitrobiphenyl was less sensitive to the residence time. These experimental results indicated the high efficiency of the homogeneous Suzuki-Miyaura cross-coupling reaction in the capillary microreactor and proved that PBA was quickly homocoupling than 4-NBDT under

Table 1 Comparison of the catalyst, the reaction temperature, the reaction time, and the yield of 4-NBP between batch process and continuous-flow process (all the solvents in both processes were MeOH)

Operate manner	Catalyst	t (h)	Yield*	Ref
Batch process	Hydroxide-Supported Palladium (0.3 mol%)	6	97%	[48]
	N-Heterocyclic Carbene-Palladium (1 mol%)	2	92%	[51]
	N-Heterocyclic Carbene-Palladium (1 mol%)	8	96%	[52]
	Pd(OAc)$_2$ (1 mol%) Ligand: C$_2$-Symmetric Thiourea	4	92%	[53]
Continuous-flow process	Pd(OAc)$_2$ (1 mol%)	0.21	99%	This work

*The yield of 4-NBP determined in all the batch processes was isolated yield

involved operational conditions. Hence, the highest 4-NBP yield of 99% was achieved with the residence time of 13 min in the capillary microreactor system.

Comparison between batch process and continuous-flow process

Table 1 shows the comparison of the catalyst, the reaction temperature, the reaction time, and the yield of 4-NBP between batch process and continuous-flow process of Suzuki-Miyaura cross-coupling reaction using 4-NBDT and PBA as reactants. All the involved processes were conducted at a mild temperature (25 °C). The reaction time in all the batch processes was longer than 2 h to achieve a high yield of 4-NBP, while the reaction time was shorted sharply to about 13 min in the continuous-flow process with the use of the capillary microreactor. In brief, the continuous-flow homogeneous Suzuki-Miyaura cross-coupling reaction in the capillary microreactor was significantly improved with a higher yield of 4-NBP, a much shorter reaction time and a lower cost of catalyst.

Conclusion

In this work, we developed two continuous-flow capillary microreactor systems to synthesize 4-nitrobiphenyl (4-NBP) from 4-nitroaniline (PNA) under mild operational conditions in separated steps, namely the diazotization of PNA to 4-NBDT and Suzuki-Miyaura cross-coupling reaction of 4-NBDT to 4-NBP. In the diazotization step, A high yield of 4-NBDT (97%) was achieved only in 2.3 s with the optimal molar ratio of HBF_4, $NaNO_2$ and PNA (i.e., 2.72:1.05:1) and reaction temperature (25 °C). The yield of 4-NBDT first increased and then decreased with the increase in the molar ratio of $NaNO_2$ to PNA, and it increased with the increase in the molar ratio of HBF_4 to PNA. The decomposition of 4-NBDT easily happened at high reaction temperatures and long residence times, indicating the importance of precise control over the reaction temperature, the residence time and the concentration of reactants. In the Suzuki-Miyaura cross-coupling reaction step, aiming to operate the reaction process in a capillary microreactor, an appropriate amount of nitric acid was used to promote the solubility of $Pd(OAc)_2$ in MeOH and to transform the reaction system into a homogeneous system. The yield of 4-NBP increased with the increase in the concentration of $Pd(OAc)_2$, the reaction temperature and the residence time. The operational conditions were optimized considering both the reaction rate and the precise control over the residence time. A high yield of 4-NBP (i.e., 99%) was obtained in just 13 min at 25 °C, and the optimal the molar percentage of $Pd(OAc)_2$ to 4-NBDT was 1 mol%. Finally, a comparison was made between the batch process and the continuous-

flow process with the use of the capillary microreactor, and the reaction efficiency was promoted with shorter reaction time and lower cost catalyst. In short, the microreactor shows excellent application potential for both the diazotization and the following Suzuki-Miyaura cross-coupling reaction. Nevertheless, there are still lots of work to be done in the future such as combining these two steps into one continuous-flow microreactor system by choosing more efficient solvents.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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