Angewandte Chemie

DOI: 10.1002/anie.200700611

Catalysis in Water

Rapid and Highly Selective Copper-Free Sonogashira Coupling in High-Pressure, High-Temperature Water in a Microfluidic System**

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C–C coupling reactions catalyzed by palladium complexes with a variety of ligands in organic solvents are commonly used for the synthesis of natural products, pharmaceuticals, organic materials, and compounds with other applications.[1–3] The organic solvents and palladium complexes are essential for dissolving the organic substances and enhancing the reaction rate.[3] However, these conventional synthetic procedures involve high levels of energy consumption for satisfactory yields to be attained and place significant limits on the reaction rates. Additionally, the separation of the catalyst and the product from the homogeneous reaction mixtures is troublesome, costly, and chemically wasteful. To overcome these problems, C–C coupling reactions in aqueous media have been investigated with the development of suitable catalysts.[4] However, reaction times of several hours are still required for the products to be formed in high yields with high selectivities.[5]

To generate large volumes of the desired products in very short reaction times with simple separation, and thus in a green process suitable for application in industry, we have developed a water-mediated approach based on "step-by-step rapid mixing and heating" in a microfluidic system[6] for the well-known Sonogashira C–C coupling reaction.[7] Our copper-free methodology involves no organic solvents and no specific ligands for the palladium catalyst.

Chemical microprocessing is generally defined as continuous flow through regular domains with characteristic dimensions of the internal structures of fluid channels, typically in the submillimeter range; an enhancement of the rate of some chemical reactions is found in a microreactor.[8–10] The schematic images in Figures 1 and 2 illustrate reactions under the conditions of step-by-step rapid mixing and heating in high-pressure and high-temperature water (HPHT-H_2O). In such a system, substrates collide and mix rapidly with an ambient aqueous solution at high pressures of around 25 MPa. The microfluidic alignment and assembly in the water flow must be controlled to begin with to cause this mixing (Figure 1 a, and micromixer 7 in Figure 2), and the resulting reaction mixture is heated rapidly to the desired high

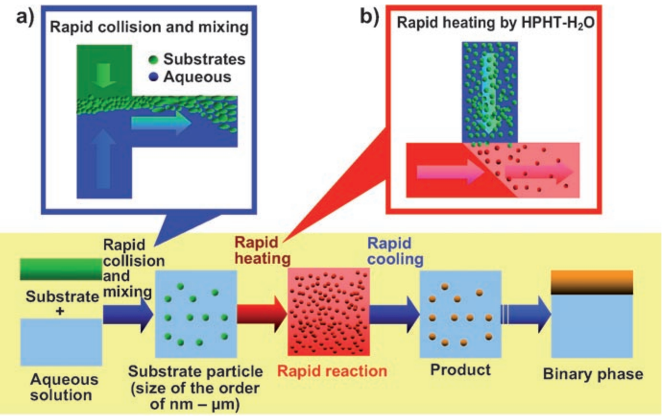

Figure 1. Schematic illustration of a reaction under the conditions of step-by-step rapid mixing and heating in high-pressure, high-temperature water.

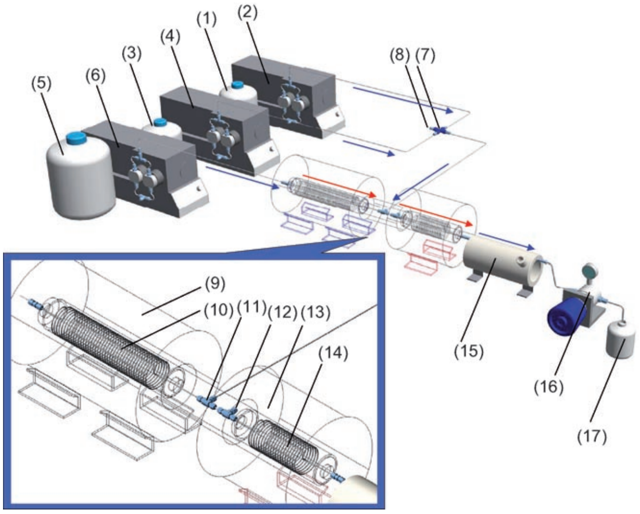

Figure 2. Diagram of the reaction setup for step-by-step rapid mixing and heating: 1) storage tank (substrates), 2, 4, 6) high-pressure liquid pumps, 3) storage tank (aqueous solution of $PdCl_2$ and NaOH), 5) storage tank (degassed distilled water), 7) micromixer, 8, 12) thermocouples, 9, 13) electric furnaces, 10) tubular coil, 11) micromixer (quick-heating part), 14) tube reactor, 15) cooler, 16) high-pressure regulator, 17) recovery tank.

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[**] This research was supported financially by the project for the "Development of Microspace and Nanospace Reaction Environment Technology for Functional Materials" of the New Energy and Industrial Technology Development Organization (NEDO), Japan.

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temperature by forcing the high-speed flow of HPHT-H_2O into the microflow processor (Figure 1 b, and micromixer 11 in Figure 2). Following the rapid heating, the reaction is completed quickly. Moreover, this water-mediated microflow processing does not require organic solvents.

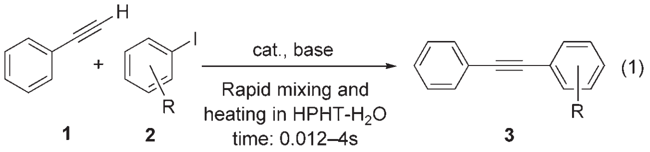
By using this strategy, the formation of particles of aggregated substrate (Figure 1 a) and their instantaneous dissolution (microscopic heterogeneity) in HPHT-H_2O (Figure 1 b) would occur to allow efficient acceleration of the reaction rate. Furthermore, with the HPHT-H_2O protocol, control of the dielectric constant (ε) is possible through adjustment of the imposed pressure and temperature.[11] Hence, organic reactants are readily made soluble or dispersive, which could make HPHT-H_2O a useful replacement for organic solvents.[12] Herein we describe the application of this high-speed and environmentally benign water-based microfluidic system to the Sonogashira coupling as a model reaction of C–C coupling, and the preparation of aryl alkynes in nearly quantitative yields within around four seconds. This approach also facilitated solvent–catalyst–product separation.

Table 1: Sonogashira coupling of aryl iodides **2** with phenylacetylene (**1**) in the presence of aqueous NaOH (2.0 M) as the base, with $PdCl_2$ (2.0 mol %) as the catalyst, under a pressure of 16 MPa, and by step-by-step rapid mixing and heating (unless otherwise indicated).

Entry	Substrate	T [°C]	t [s]	Yield [%]	Selectivity [%]	TOF [h^{-1}]
1	**2a**: R = H	250	0.012	1.5	100	7.7×10^4
2	**2a**	250	0.025	87	100	3.9×10^6
3	**2a**	250	0.035	96	100	4.3×10^6
4	**2a**	250	0.1	99	100	1.6×10^6
5	**2a**	200	0.1	14	99	2.5×10^5
6	**2a**	225	0.1	37	98	6.7×10^5
7	**2a**	275	0.1	79	99	1.4×10^6
8	**2a**	300	0.1	83	98	1.5×10^6
9[a]	**2a**	250	4	89	92	8.0×10^4
10	**2a**	250	4	99	100	4.4×10^4
11[b]	**2a**	250	4	92	99	2.0×10^4
12[c]	**2a**	250	120	34	63	1.0×10^1
13	**2b**: R = 4-CH_3	250	0.1	90	100	1.6×10^6
14	**2c**: R = 4-CH_3O	250	0.1	91	99	1.6×10^6
15	**2d**: R = 4-NH_2	250	0.1	92	100	1.7×10^6
16	**2e**: R = 4-HO	250	0.1	88	98	1.6×10^6
17	**2f**: R = 3-CF_3	250	0.1	99	100	1.8×10^6
18	2-iodothiophene (**4**)	250	0.1	98	99	1.8×10^6
19	1-iodonaphthalene (**5**)	250	1.0	81	97	1.5×10^5
20[c–e]	**2a**	70	1800	62	–	2.5×10^2
21[c,e,f]	4-chloroiodobenzene (**6**)	100	3600	100	–	1.0×10^3
22[f,g]	**6**	120	300	96	–	1.2×10^4

[a] $PdCl_2$ (1.0 mol %) was used as the catalyst. [b] $PdCl_2$ (4.0 mol %) was used as the catalyst. [c] Two-phase reaction. [d] Ethyldiisopropylamine was used as the base and $[PdCl_2(PPh_3)_3]$ (0.5 mol %) was used as the catalyst.[7f] [e] The reaction was performed under a pressure of 0.1 MPa. [f] A palladium(II) chloride complex derived from (dipyridin-2-yl)methylamine (0.1 mol %) was used as the catalyst, pyrrolidine (2 equiv) was used as the base, and tetrabutylammonium bromide (1.0 equiv) was included as an additive.[7g]. The maximum TOF value reported in reference [7g] is 6.7×10^4 h^{-1}. [g] Microwave irradiation.

The Sonogashira coupling was investigated under various conditions by using the approach of step-by-step rapid mixing and heating [Eq. (1)]. As a starting point for the development of our methodology, we studied the reaction of phenylacetylene (**1**) with iodobenzene (**2a**; Table 1, entries 1–11). Diphenylacetylene (**3a**) was obtained in nearly quantitative yield after reaction times of only 0.1–4.0 s at 250 °C and 16 MPa in the presence of $PdCl_2$ (2 mol %) as the catalyst and NaOH (2 M) as the base (Table 1, entries 4 and 10). No homocoupling of **1** or **2a** was observed.[13] Even with a shorter reaction time of 0.035 s, **3a** was formed in > 96 % yield (Table 1, entry 3). The yield of **3a** decreased to 1.5 % when the reaction time was decreased to 0.012 s (Table 1, entry 1) as a result of diffusion control of the reaction rate; however, 100 % selectivity for the formation of **3a** was still observed. At the end of the reaction, the desired product was floating on the surface of the aqueous solution, whereas most of the $PdCl_2$ catalyst had precipitated as metallic Pd^0. Therefore, the product could be isolated readily either by phase separation or by filtration.



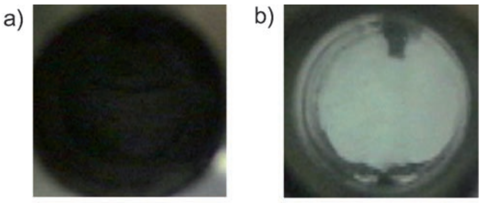
(1)

Up to 250 °C, an increase in the temperature led to an increase in the yield; the yield then decreased significantly to approximately 80 % at 275 °C or above. However, close to 100 % selectivity for **3a** was observed in all cases (Table 1, entries 4–8). Subsequent experiments were carried out at various concentrations of $PdCl_2$ (Table 1, entries 9–11). The best result was obtained with the lower catalyst loading of 2.0 mol %, rather than at the higher concentration of 4.0 mol %. We also attempted the Sonogashira coupling reaction without using the method of step-by-step rapid mixing and heating. This experiment was performed in a binary phase of $PdCl_2$ dissolved in water and the substrates in a closed batch reactor (Table 1, entry 12). The product **3a** (R = H) was formed in only 34 % yield in 120 s at 250 °C and 16 MPa. Thus, the method of step-by-step rapid mixing and heating was found to be key to the substantial reaction-rate acceleration and improvement in selectivity observed in this study for the Sonogashira reaction.

Recent studies showed that palladium complexes with organoamines are effective catalysts for the Sonogashira coupling in water (Table 1, entries 20–22).[7f,g] A turnover frequency (TOF) of 2.5×10^2 h^{-1} was observed with this method for the production of **3a** in water (Table 1, entry 20).[7f] Furthermore, a TOF of 1.0×10^3 h^{-1} was observed for the coupling between **1** and 4-chloroiodobenzene (**6**; Table 1, entry 21).[7g] When this system was also irradiated with microwaves, the TOF increased to $1.2\times10^4\ \mathrm{h}^{-1}$ (Table 1, entry 22).[7g]

Amazingly, with our approach of step-by-step rapid mixing and heating, we observed a maximum TOF of $4.3\times10^6\ \mathrm{h}^{-1}$ (Table 1, entry 3). We tested a wide range of aryl iodide derivatives, such as 4-iodotoluene (**2b**), 4-methoxyiodobenzene (**2c**), 4-iodoaniline (**2d**), and 4-iodophenol (**2e**), in the reaction with **1** (Table 1, entries 13–16). Very high TOFs of up to $1.7\times10^6\ \mathrm{h}^{-1}$ were observed. Furthermore, Sonogashira coupling reactions of **1** with other aryl iodides, such as 3-iodo(trifluoromethyl)benzene (**2f**), 2-iodothiophene (**4**), and 1-iodonapthalene (**5**), also proceeded with high TOFs to give the desired products in high yields (Table 1, entries 17–19).

To gain more information about the origin of the reaction-rate acceleration, we investigated the phase behavior of the mixtures of **1**, **2a**, and pure water at 50 and 250 °C at a pressure of 16 MPa (that is, of the solutions inside the micromixers) by using a view cell (Figure 3 a,b).[14] The substrate dispersion changed from black and opaque to colorless and transparent upon an increase in the temperature from 50 to 250 °C. The substrate molecules fall out of solution and form substrate particles during their residence in the tube at the lower temperature (Figure 3 a). The average particle size of the substrate was determined to be approximately 44 μm by the light-scattering method. It was confirmed that the particles are dissolved in HPHT-H_2O at 250 °C and 16 MPa (Figure 3 b). Thus, the formation of a homogeneous phase in the micromixer was ascertained. The microscopic heterogeneity in HPHT-H_2O results in efficient acceleration of the reaction rate. Recently, the vigorous mixing of aqueous–organic biphasic reaction systems was reported to result in fast reactions of insoluble organic reactants. The reactions appear to take place at the surface of substrate particles in the suspension generated by the vigorous shaking.[15]



50 °C, 16MPa 250 °C, 16MPa

Figure 3. Photographs taken through a view cell of the phase behavior of the mixture of substrates **1** and **2a** under each set of conditions.

Figure 4 shows the background-corrected FT-IR absorption spectra of the mixtures of substrates **1** and **2a** and water at 50 and 250 °C and 16 MPa. The spectra recorded at 250 °C (black line) contain new intense bands at 3303 and 1572 cm^{-1}, which can be assigned to acetylenic C–H stretching (ν_1) and C–H out-of-plane bending (δ_s) of dissolved **1** and **2a**, respectively.[16] However, these peaks become weaker or almost disappear at 50 °C. Thus, it was confirmed that the substrates were soluble in H_2O in the HPHT region. The formation of a homogeneous phase results from the higher solubility induced by the dielectric constant and the higher diffusibility induced by turbulent flow (Reynolds number ≤ 3600). The formation of particles of high aspect ratio may be explained by the smaller deviations in fluidic alignment in the microchannel because of a shear force acting on the water molecules at the surface of the substrate particles. Water–substrate interactions could be modified chemically under the conditions of step-by-step rapid mixing and heating with useful consequences for the control of chemical reactivity. A few examples of the direct observation by IR spectroscopy of molecular complexes of a solute with a solvent have been described.[17] The IR spectra in Figure 4 reveal the formation of a hydrogen bond between the oxygen atom of H_2O and the terminal hydrogen atom of **1**. The C–H stretching vibration of **1** is red shifted by 20 cm^{-1} upon complexation with H_2O, whereas the C–H out-of-plane bending of **2a** does not shift. This result suggests strongly the occurrence of an appreciable interaction between the terminal hydrogen atom of **1** and the H_2O molecules. Moreover, in the HPHT region, water molecules act like a catalyst and transfer protons along locally formed hydrogen bonds,[18] which leads to a lowering of the activation energy for bond cleavage and bond formation.[19] The role of water in intermolecular hydrogen-atom transfer has also been supported by quantum-chemical calculations.[20]

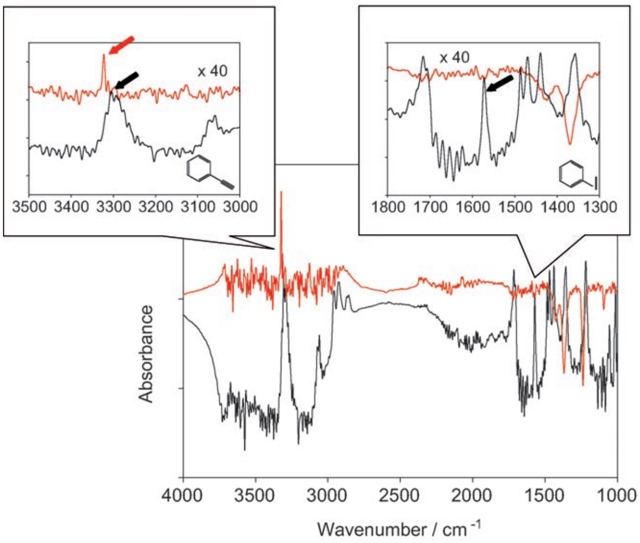


Figure 4. Background-corrected IR absorption spectra of substrates **1** and **2a** in water at 50 °C and 16 MPa (red line) and 250 °C and 16 MPa (black line) in the absence of $PdCl_2$. The background was corrected on the basis of pure water at 50 °C and 16 MPa. The insets show the C–H streching band (left) and the C–H out-of-plane bending band (right) enlarged and shifted.

In conclusion, we have developed a water-mediated reaction system on the basis of "step-by-step rapid mixing and heating" and demonstrated that it can be applied to the Sonogashira coupling to generate the desired products very rapidly in nearly quantitative yields. More specifically, the products are obtained in quantitative yields within only around 4 s in the presence of a ligandless $PdCl_2$ catalyst in pure water at 16 MPa and 250 °C. No organic solvent or cocatalyst is required. Exceptionally high turnover frequencies of up to 4.3×10^6 h^{-1} were observed for the Sonogashira coupling reaction with our system. Moreover, the desired products remained on the surface of the aqueous solution, and the catalyst was deposited as Pd^0. Thus, the products could be isolated readily either by phase separation or by filtration.

Received: February 9, 2007

Keywords: C–C coupling · high-pressure chemistry · high-temperature chemistry · microreactors · water chemistry

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