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Promoting the catalytic efficiency of a catalyst by a solvothermal method[†]

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A solvothermal method has been successfully introduced and applied to catalytic organic reactions. This method provides an easy way to promote catalyst efficiency. Several classical coupling reactions and aminations of aryl halides were performed using common catalysts such as commercial Pd/C and Cul using this method.

Palladium-catalysed carbon-carbon (C-C) coupling reactions, such as the Suzuki-Miyaura, Heck, Sonogashira and Ullmann reactions, and copper-catalysed carbon-nitrogen (C-N) coupling reactions, such as the amination of aryl halides, are important and effective methods of introducing functional groups in organic synthesis. Besides the traditional methods of conducting the experiments in a flask over a catalyst with heating, several novel synthetic methods, such as photocatalysis methods,¹ microwave methods,² electrocatalysis methods,³ and supercritical methods,⁴ have been developed and demonstrated satisfactory results. What's more, some transition-metal free reactions^{5,6} and ligand-free reactions^{7–9} have also been reported. Although the previously mentioned methods are effective, an easier and more efficient method is still desired. For a catalytic reaction, the most common way to control the reaction process is by changing factors such as the temperature, pressure, catalyst or electromagnetic wavelength as well as the solvent, which may have a conspicuous effect on both the chemical thermodynamics and dynamics of the reaction. Catalysts and their mechanisms have been systematically studied and applied with great success.^{10,11} To improve the catalytic ability of metal catalysts, such as palladium, platinum and copper, using ligands and decreasing the catalyst size to a nanometre scale are effective methods.¹²⁻¹⁵ However, these methods usually cost a lot of money because of the use of expensive ligands, precursors, surfactants and take much time because of complex preparation processes. Of all the factors mentioned above, temperature is the easiest and most convenient to control. However, temperature control is usually limited by the boiling point of the solvent, that is, the optimized reaction temperature and the boiling point of the solvent do not necessarily correlate. For example, water will reflux in a flask at 100 °C at atmospheric pressure and cannot rise to 170 °C. To solve this problem, a solvothermal method is considered to be a good solution. Solvothermal methods have already been widely used in the synthesis of many inorganic materials, such as metals, metallic oxides, metallic sulphides and coordination compounds as well as molecular sieves.^{16–25} However, to the best of our knowledge, there are no examples of performing different types of organic coupling reactions under solvothermal conditions. Herein we report examples of several classical organic reactions, such as Suzuki, Heck and Sonogashira couplings, and amination of aryl halides, over common, cheap palladium or copper catalysts under solvothermal conditions.

Initially, we focused on the Suzuki–Miyaura coupling reaction. A series of systematic work on Suzuki–Miyaura coupling in aqueous media has been undertaken since Toshikazu first reported his work in 2002.^{26,27}

In some publications, for example by Choudary and co-workers in 2002,²⁸ the actual reaction temperature didn't meet the desired reaction temperature. They used a mixture of dioxane and water as the solvent and set the temperature to 100 °C. However, the boiling point of this solvent is only 87.8 °C. Thus what we are most concerned with in this work is finding a general method that could solve this problem rather than a specific solvent or system.

As for the solvothermal method, firstly the solvent was taken into account (Table 1). Solvent selection is more flexible for solvothermal methods and any solvent that would not hinder the reaction could be a possible solvent in theory. To give a brief comparison, the control experiments conducted in a flask are also listed in Table 1. We can see that in either water or ethanol, an enhanced yield is achieved under solvothermal conditions compared to those reactions conducted in a flask. The highest yields were achieved from the reactions in the mixed solvent, under both the standard and solvothermal conditions.

Thus in order to highlight the fact that the solvothermal method can promote the catalytic efficiency of a catalyst, a single solvent should be used. Since water is cheap, green and abundant,

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 Table 1 Commercial Pd/C-catalyzed Suzuki–Miyaura coupling of bromotoluene and phenylboronic acid: effect of solvent choice on the reaction yield^a

| Br + B(OH) ₂ Commercial Pd/C solvent, autoclave | | | | | | |
|---|-------------------------|-------------------------|----------------|--|--|--|
| Entry | Solvent | Actual temperature (°C) | Yield $(\%)^b$ | | | |
| 1 | water | 130 | 82 | | | |
| 2 | ethanol | 130 | 78 | | | |
| 3 | water : ethanol = $1:1$ | 130 | 95 | | | |
| 4^c | water | 100 | 71 | | | |
| 5 ^c | water | 70 | 58 | | | |
| 6 ^{<i>c</i>} | ethanol | 78.4 | 63 | | | |
| 7 ^{<i>c</i>} | water : ethanol = $1:1$ | 78.1 | 92 | | | |

^{*a*} Reaction conditions: bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), K_2CO_3 (1.5 mmol), TBAB (0.12 mmol), solvent (2 mL), and commercial Pd/C catalyst (0.6 mol%), 130 °C, 2 h, solvothermal treatment. ^{*b*} Yields were determined by GC. ^{*c*} Conducted in a flask.

we chose it as the example solvent for the following experiments. We investigated the scope of aryl halides that could react with phenylboronic acid under hydrothermal conditions and performed control experiments. As shown in Table 2, we can see that for aryl bromides, the substrates examined under optimal conditions achieved good yields under solvothermal treatment while the aryl chlorides achieved lower yields. When compared with the control experiments which were run in flasks, the hydrothermal method clearly promotes the catalytic efficiency. It should be noted that the solvothermal method activates the aryl chlorides by simply increasing the reaction temperature. The substituted aryl halides with electron-withdrawing and electrondonating groups reacted smoothly. Aryl halides with a substituent at different sites on their benzene rings had different activities. Due to steric hindrance, substituents at the ortho-position would hinder the coupling process thus giving a lower yield. What's more, this method can be expanded to other aromatic compounds, such as pyridine.

The palladium catalyst used in the experiments is a common commercially available Pd/C catalyst and could be easily dispersed in an aqueous phase, but cannot be easily dispersed in an oil phase. Therefore the Pd/C catalyst can be easily recycled after extraction by simple filtration. We recycled the Pd/C catalyst three times and its catalytic performance is shown in Table S1, ESL† We can see that even the commercial Pd/C catalyst can be reused at least twice. The gradual decrease in the yield is due to loss of the Pd/C catalyst during the filtration step when using normal filter papers.

We then tried to extend this method to some other important reactions. As shown in Table 3, the commercial Pd/C catalyst can also catalyze Heck and Sonogashira coupling reactions. To summarise, the solvothermal method is a suitable and generalized method for improving the yield of C–C coupling reactions.

Furthermore, we were curious about whether the hydrothermal method could be applied to C–N bond forming reactions and we chose the amination of aryl halides as the model reaction. Firstly the reaction parameters were optimized (see Table S2, ESI†). The

| Table 2 Commercial Pd/C-catalyzed Suzuki–Miyaura coupling of aryl halides |
|---|
| with phenylboronic acid under hydrothermal conditions ^a |

| R | X+ | DH)2 H20, autoclave | |
|-------|---|---|------------------------|
| Entry | Aryl halide | Product | Yield (%) ^b |
| 1 | MeO-Br | MeO | 92 (64) |
| 2 | o Br | $\sim \sim $ | 92 (51) |
| 3 | Br NH ₂ | | 42 (37) |
| 4 | OHC | онс | 82 (45) |
| 5 | ————Br | | 96 (10) |
| 6 | Br | | 67 (49) |
| 7 | ⟨Br | = | 52 (30) |
| 8 | | | 29 (N.R.) |
| 9 | CI | | 10 (N.R.) |
| 10 | | 0 ₂ N- | 26 (N.R.) |
| 11 | MeO | MeO- | 65 (N.R.) |
| 12 | онсСІ | OHC | 61 (N.R.) |
| 13 | ° ———————————————————————————————————— | \sim | 76 (N.R.) |

^{*a*} Reaction conditions: aryl halide (0.5 mmol), phenylboronic acid (0.75 mmol), K_2CO_3 (1.5 mmol), TBAB (0.12 mmol), water (2 mL), and commercial Pd/C catalyst (0.6 mol%), 130 °C, 2 h for aryl bromides and 4 h for aryl chlorides, hydrothermal conditions. Control experiment conditions: 100 °C in a flask under atmospheric pressure. ^{*b*} Yields of the isolated products. Yields of the control experiments are in parentheses. N.R. represents no reaction.

optimal reaction conditions are as follows: $NH_3 \cdot H_2O$ as the base, coordinating agent and reactant, water as the solvent, CuI as the catalyst and a reaction temperature of 200 °C.

 Table 3 Different types of coupling reactions performed under solvothermal conditions^a

| Enti | y Reaction type | e Reactant 1 | Reactant 2 | 2 Product | Yield $(\%)^b$ |
|------|-----------------|---------------------------------|------------|-----------|----------------|
| 1 | Heck | | ⟨Br | Ph Ph | 62 |
| 2 | Heck | $\operatorname{A}_{\mathrm{A}}$ | | | 86 |
| 3 | Sonogashira | | | | >74 |
| 4 | Sonogashira | | Br | | \rangle^{11} |

^{*a*} Heck reaction conditions: Reactant 1 (0.55 mmol), reactant 2 (0.5 mmol), K₂CO₃ (1.5 mmol), TBAB (0.12 mmol), dioxane (2 mL), commercial Pd/C catalyst (0.6 mol%), 130 °C, 2 h, solvothermal conditions. Sonogashira reaction conditions: Reactant 1 (0.55 mmol), reactant 2 (0.5 mmol), K₂CO₃ (1.5 mmol), Et₃N (1 mL), THF (1 mL), commercial Pd/C catalyst (0.6 mol%), CuI (0.4 mmol), 130 °C, 2 h, solvothermal conditions. ^{*b*} Yield of isolated product.

Next we investigated the scope of aryl halides that can be transformed into primary amines under hydrothermal conditions and also performed control experiments. As shown in Table 4, we can see that for both aryl bromides and aryl chlorides, most of the substrates achieved good yields under hydrothermal conditions, which greatly surpass the yields of the control experiments.

Similar to the coupling reactions mentioned above, the substituted aryl halides with electron-withdrawing or electrondonating groups, and those with different functional groups at different sites, gave satisfactory yields. Despite the steric hindrance, the presence of substituents has a more prominent influence on the activity of the substrates. In addition, the substrates can be expanded to include other aromatic compounds, such as pyridine which resulted in a good yield. Compared with using complex coordinating reagents, organic solvents and other additives, the hydrothermal system only uses water, ammonia, cuprous iodide and heat. Ammonia plays multiple important roles thus greatly simplifying the system. Moreover, the ammonia will not evaporate because the autoclave is sealed. As is known, both ammonia and cuprous iodide are cheap and abundant chemical reagents and water is a green solvent. Therefore this approach provides a simple way to cheaply synthesize primary amines.

To better understand the mechanism of the hydrothermal method, we chose 4-bromoanisole as a cross-coupling substrate to investigate the process. We performed experiments at seven different temperatures, from 25 °C to 170 °C, bearing in mind that the boiling point of water is 100 °C, and we prolonged the reaction time to 8 h. Control experiments below 100 °C were also conducted in flasks.

As shown in Table 5, the yield fluctuates with increasing temperature. When the temperature is 25 $^{\circ}$ C, the yield of the

| Table 4 | Amination | of aryl | halides | under | hydrothermal | conditions ^a |
|---------|-----------|---------|---------|-------|--------------|-------------------------|
|---------|-----------|---------|---------|-------|--------------|-------------------------|

| | ${\underset{R}{}{}} {\underset{NH_3}} H_2 O$ | Cul H ₂ O, autoclave | -NH ₂ |
|-------|--|------------------------------------|------------------|
| Entry | Aryl halide | Product | Yield $(\%)^b$ |
| 1 | Br | NH ₂ | 95 (N.R.) |
| 2 | MeO-Br | MeO-NH2 | 91 (N.R.) |
| 3 | о —————————Вг | | 89 (N.R.) |
| 4 | Br NH ₂ | NH ₂ NH ₂ | 18 (N.R.) |
| 5 | —————————————————————————————————————— | | 88 (N.R.) |
| 6 | Br | | 90 (N.R.) |
| 7 | Br Br | NH ₂ | 56 (N.R.) |
| 8 | O ₂ N-CI | O2N-NH2 | 74 (N.R.) |
| 9 | | | 69 (N.R.) |
| 10 | CI | | 71 (N.R.) |
| 11 | CI CI | | 65 (N.R.) |
| 12 | MeO-CI | MeO-NH2 | 58 (N.R.) |
| 13 | H ₂ N CI | NH ₂ | 54 (N.R.) |

^{*a*} Reaction conditions: aryl halide (0.5 mmol), NH₃·H₂O (3.0 mmol), water (2 mL), and CuI (5 mol%), 200 °C, 2 h, hydrothermal conditions. Control experiment conditions: 100 °C in a flask under atmospheric pressure. ^{*b*} Yields of isolated products. Yields of the control experiments are in parentheses. N.R. represents no reaction.

reaction in the autoclave (Fig. 1) was lower because there was no stirring process to mix the reactants together. When the temperature was raised to 70 $^{\circ}$ C and 90 $^{\circ}$ C, the yields of the reactions in the two different tanks were almost the same. On one hand, this substrate has high intrinsic activity, and on the other

Table 5 Effect of temperature on the hydrothermal cross -coupling reaction^a

| $T (^{\circ}C)$ Yield (%) ^b | 25 | 70 | 90 | 110 | 130 | 150 | 170 | | |
|--|---------|---------|---------|-----|-----|-----|-----|--|--|
| | 20 (40) | 75 (72) | 98 (95) | 81 | 94 | 98 | 87 | | |
| ^{<i>a</i>} Reaction conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.75 mmol) K CO (1.5 mmol) TBAB (0.12 mmol) water (2 | | | | | | | | | |

acid (0.75 mmol), K_2CO_3 (1.5 mmol), TBAB (0.12 mmol), water (2 mL), and commercial Pd/C catalyst (0.6 mol%), 8 h, hydrothermal conditions. ^{*b*} Yields were determined by GC, yields of control experiments are in parenthesis.

hand, when the reaction temperature is high, convection in the autoclave, like stirring in a flask, results in mass transfer. Initially, we ran the experiment at 25 °C in a flask and it gave a 40% yield of the expected product. However, there is the same amount of the self-coupling product of phenylboronic acid, biphenyl, in solution. At 70 °C, although the yield is still low, which is due to the slow reaction rate at low temperature, no byproduct is formed under hydrothermal conditions. When the temperature was increased to 90 °C, the yield was almost 100% due to a faster reaction rate. However, the yield decreased obviously at 110 °C. According to the GC-MS analysis result, a small amount of biphenyl appeared again, which indicates that the side reaction could occur at 110 °C. When the temperature was increased to 130 °C or 150 °C, we observed that the yield is nearly 100% again. This demonstrates that the hydrothermal method can restrain side reactions at suitably high temperatures. We inferred that the C-Br bond of the substrate was activated, thus decreasing the activation energy of the cross-coupling reaction, which has the advantage of increasing the reaction rate of the desired reaction over that of the side reaction. Furthermore, the yield decreased again when the temperature was increased to 170 °C. According to the GC-MS analysis result, the byproducts included not only biphenyl but also 4,4'-dimethoxybiphenyl. The latter product is the self-coupling product of 4-bromoanisole. This result indicates that the substrate is over activated and this supports the previous assumption. Furthermore, the optimised conditions for the amination of aryl halides also indicate that when the reaction temperature is higher than the boiling point of the solvent, the hydrothermal method demonstrates a good performance (see Table S2, ESI[†]). Any given



Fig. 1 A Teflon lined autoclave. The three parts: the stainless steel cap, the outer stainless steel shell and the inner Teflon liner. (left, 40 ml; right, 10 ml).

substrate has its own optimal reaction temperature, which may be higher or lower than the boiling point of the solvent. For those whose optimal temperature is higher than the boiling point of the solvent, such as chlorobenzene, the solvothermal method provides an easy way to improve its reactivity.

In summary, we have successfully applied a solvothermal method to organic synthesis. This method is a generalized way to realize C–C and C–N bond formation and can promote the catalytic efficiency of catalysts. The advantages of the solvothermal method are as follows: the experiments are easy to perform; the choice of solvent is flexible; the reaction system is simple, without the need for expensive catalysts and complex ligands; the reactions occur with a common catalyst; the use of a sealed system means that it is easy to perform oxygen-sensitive reactions and prevent volatile compounds from evaporating. The good functional group tolerance under solvothermal conditions indicates that this method can be extended to some other reactions.

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