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Product Selective Reaction Controlled by the Combination of a Palladium Nanoparticles, Continuous Microwave Irradiation, and a Co-existing Solid; Ligand-Free Buchwald–Hartwig Amination vs Aryne Amination

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Abstract: We have developed a continuous microwave irradiation-assisted Buchwald–Hartwig amination using our original Pd nanoparticle catalyst with copper plate as a co-existing metal solid. In this methodology, a microwave-controlled product selectivity was achieved between Buchwald–Hartwig amination and aryne amination performed under strongly basic conditions and a high reaction temperature, because a polar chemical species such as Ar–Pd–halogen might be activated selectively by microwave radiation. Moreover, our catalyst could be used repeatedly over 10 times, and the amount of Pd leaching could be suppressed to a low level.

Introduction

Arylamines are widely utilized as functional organic materials in fields such as pharmaceuticals, agrochemicals, dyes, and polymers. Among methodologies for convenient synthesis of arylamines, carbon–nitrogen bond forming reactions are very important.[1] The Pd-catalyzed cross-coupling of tin amides and aryl halides to generate arylamines in homogenous systems was first studied by Migita and colleagues in 1983.[2] Following by this report, the Buchwald and Hartwig groups developed a Pd-catalyzed amination under relatively mild reaction conditions independently.[3, 4] However, sophisticated dialkylaryl phosphate ligands are often used to promote these reactions.[1] To develop the ligand-free and environmentally benign metal-catalyzed coupling reaction, metal nanoparticle (NP) catalysts have been widely used to catalyze the coupling reaction.[5] We have also developed the Pd NP catalysts immobilized on gold or glass and applied them to organic reactions.[6] Although many examples of Suzuki–Miyaura coupling, Heck reaction, Sonogashira coupling have been reported,[7] Buchwald–Hartwig amination catalyzed by metal NPs catalyst were reported in only 13 examples (Figure 1a).[8] Moreover, the catalysts using...
in 13 examples have four drawbacks: 1) ligand addition, 2) inconvenient removal of NPs, 3) insufficient recyclability of NP catalysts (up to six times), and 4) a few reports about leaching analysis of NPs.

On the other hand, external energy-assisted (visible light, microwave) organic synthesis has been enthusiastically researched to achieve reactions that are difficult or impossible and to access eco-friendly methodologies.[9] Among them, a microwave radiation has been applied for the metal NP-catalyzed coupling reaction (Suzuki–Miyaura coupling, Ullmann coupling, Heck reaction).[10] Conventional microwave machine which was used in previous report turns off within a very short period when the temperature limit was reached and cannot use microwave efficiently. Therefore, we developed the continuously irradiation type microwave machine, then we have reported continuous microwave irradiation-assisted ligand-free Suzuki–Miyaura coupling of inert aryl chlorides using a Ru NP catalyst on sulfur-modified gold (henceforth referred to as SARu) or a Pd NP catalyst on sulfur-modified glass (henceforth referred to as SGIpPd).[11] In the latter case, it is unique that the addition of solid metal promotes the reaction due to increased microwave absorption of the reaction system (Figure 1b).[12] We wondered whether this methodology could apply to Buchwald–Hartwig amination.

Herein, we report the first example of continuous microwave irradiation-assisted ligand-free Buchwald–Hartwig amination using a Pd NP catalyst and co-existing solid metal (copper plate, Figure 1c), and we also found that this combination can work together to control the product selectivity to give only a Buchwald–Hartwig amination product.

Results and Discussion

In the beginning, we attempted the ligand-free Buchwald–Hartwig amination between aryl bromides and morpholine (2a) using SGIpPd,[13] without microwave irradiation under the conditions quoted (Table 1). Regioisomers were obtained from 1a, 1b, 1c, 1d respectively because an aryne was generated by strongly basic conditions and high temperatures[14] (entries 1–4).

Therefore, we investigated the optimization of reaction conditions to prevent the generation of regioisomers (Table 2). When the reaction was carried out at lower temperatures such as 80 or 90 °C, the corresponding coupling product was barely formed (entries 1 and 2). Moreover, the regioisomer was formed by heating at 100 °C (entry 3); hence the reaction using continuous microwave irradiation was carried out at temperatures lower than 90 °C. The substrates were heated to 80 or 90 °C under microwave irradiation for 24 h (entries 4 and 5). Even though the yield was improved, it hit the ceiling of 36%. We considered that this might be because a large amount of Pd was leached and aggregated and so lose its catalytic activity. Then, we conducted the reaction in two steps and removed the SGIpPd between the first step and second step, as shown in the equation in Table 3. The reaction mixture was heated for a short time to elute the Pd NPs into the reaction system (1st step) then heated for a long time to effect the reaction. The yield was slightly increased with longer reaction time, and higher microwave power and temperature (entries 1–4). When the reaction was carried out with an aluminum foil which is effective for Suzuki–Miyaura coupling of aryl chlorides based on our previous work,[11b] the corresponding coupling product was obtained in just only 11% yield (entry 5). It is because aluminum foil decayed under the strongly basic conditions, and the microwave absorption in the reaction system was not increased. Therefore, we used copper plates instead of aluminum foil as the co-existing metal, and we found that the yield of the product improved to 64% (entry 6). Encouraged by these results, we continued our experiments to optimize the equivalence of reagents and the reaction time of the first and second steps (entries 7 and 8); and finally, we found that the coupling product was obtained in 90% yield under the conditions indicated in entry 9.[15] When the reaction was performed under the conditions of entry 9 without microwave irradiation, the product was not obtained (entry 10). In addition, the reaction did not proceed with only Cu plate as metal source (entry 11). According to this result, Pd is active species for the reaction, but Cu is not (example of Cu-catalyzed C-N coupling, see ref 6f). Subsequently, we investigated the reusability of SGIpPd for the Buchwald–Hartwig amination. When the SGIpPd was used repeatedly 10 times in the reaction under the optimal conditions, the coupling product in each case was obtained in high yield (Table 4). In addition, the amount of Pd leaching into each reaction solution was measured by inductively coupled plasma mass spectrometry (ICP-MS; Table 4).

Table 1. Buchwald-Hartwig amination of some aryl bromides catalyzed by SGIpPd under conventional heating.

| Entry | Ar-Br | Yield (%) |
|-------|-------|-----------|
| 1     | MeO   | 3 position : 41 |
| 2     | Br    | 1 position : 22 |
| 3     | Br    | 3 position : 59 |
| 4     | Br    | 3 position : 30 |

[a] The reaction was performed for 7 h.
Table 2. Optimization of reaction conditions for the reaction of aryl bromide (single step).

| Entry | Temp. (°C) | cont. MW (W) | Yield (%) |
|-------|------------|--------------|-----------|
| 1     | 80         | –            | ND        |
| 2     | 90         | –            | 5         |
| 3     | 100        | –            | 9         |
| 4     | 80         | 50           | 12        |
| 5     | 90         | 50           | 36        |

ND = Not detected. N = 4-morphorinyl.

Next, SGlPd was used repeatedly for the Buchwald–Hartwig amination between several aryl bromides 1 and morpholine (2a) to give eight different types of products (Sequential re-use of SGlPd; Table 5).

This was also the case when the amines were changed. SGlPd was also repeatedly used for the Buchwald–Hartwig amination of 4-bromoanisole (1a) with several amines 2 (Table 6). Every corresponding coupled products were obtained in around 90% yield.

Ligand-free Buchwald-Hartwig amination between aryl chlorides and amines using SGlPd

Next, we investigated the Buchwald–Hartwig amination of aryl chloride as a more inert compound than aryl bromides. At first, the SGlPd was utilized for the reaction under the conditions as described in Table 1. In addition to the desired product, regioisomer were also obtained in low yield. Next, the optimal reaction conditions for aryl bromides (entry 9, Table 3) were utilized for the Buchwald–Hartwig amination of 4-chloroanisole (4a) and morpholine (2a; Scheme 2). However, the desired coupled product 3aa was obtained in only 43% yield and the 4-chloroanisole remained.

Therefore, we continued our experiments to determine appropriate reaction conditions for the Buchwald–Hartwig amination of aryl chlorides and amines. We changed each condition in both step 1 and step 2; finally, we found the experimental conditions as outlined in the equation in Table 7, in which amine 2a was added in the second step. When the reaction temperature was higher, the yield of 3aa was higher (100 °C: 59% yield).
a) SGIPd was not used for the reaction, ND = Not detected. N = 4-morphoriny

120 °C : 75%, 130 °C : 78%, entries 1–3). However, when the reaction was carried out at 130 °C, the regioisomer 3aa' via the aryne intermediate was obtained in 5% yield (entry 3). Next, we investigated the reaction time for the first step (entries 4–8). When the reaction was performed for 3 h, the yield of the desired product was decreased to 61% (entry 4). It was considered that a large number of Pd NPs leached into the reaction solution were agglomerated and deactivated. Moreover, a shorter reaction time, such as 60–80 min, also decreased the yield of product between 73–78% respectively, because amount of Pd NPs leached into the reaction system was not enough for this reaction to proceed (entries 6–8). When the reaction was performed for 1.5 hours in the 1st step, the product was obtained in 81% yield (entry 5).

From the above results, we investigated the substrate scope of aryl chlorides and amines under the optimum conditions (entry 8, Table 7). When chlorobenzene (4b) or 4-chloroanisole (4a) was subjected to the reaction with amines such as morpholine 2a, N,N-dibutyramine (2j), benzylamine (2k) or N,N-dicyclohexylamine (2f), the corresponding coupled products, were obtained in good yields, respectively (entries 1–7, Table 8).

Based on the generally known effect of microwave irradiation on compounds with a dipole moment and the experimental results of the product selective formation of the desired coupled product under continuous microwave irradiation, we proposed the plausible reaction mechanism (Figure 1). In conventional heating at high temperature, not only the typical Buchwald–Hartwig amination but also the carbon–nitrogen bond forming reaction via an aryne intermediate (M1) proceeded.

**Table 4.** Repeated use of catalyst and Pd leaching into the reaction mixture.

| Run | Yield (%) | Leached Pd (μg) | Leached Pd (mmol%) |
|-----|-----------|----------------|---------------------|
| 1   | 92        | 0.26           | 1.44                |
| 2   | 90        | 0.15           | 0.84                |
| 3   | 91        | 0.23           | 1.29                |
| 4   | 89        | 0.23           | 1.28                |
| 5   | 89        | 0.31           | 1.69                |
| 6   | 88        | 0.25           | 1.40                |
| 7   | 86        | 0.28           | 1.57                |
| 8   | 86        | 0.33           | 1.84                |
| 9   | 86        | 0.15           | 0.83                |
| 10  | 84        | 0.27           | 1.52                |

[a] The average of three sample.

**Table 5.** Sequential re-use of SGIPd (scope of aryl bromides).

| Run | Ar–Br | Yield (%) | Run | Ar–Br | Yield (%) |
|-----|-------|-----------|-----|-------|-----------|
| 1   | 1e    | 3ea, 98   | 5   | 1b    | 3ba, 93   |
| 2   | 1f    | 3fa, 97   | 6   | 3c    | 3ca, 87   |
| 3   | 1g    | 3ga, 90   | 7   | 1h    | 3ha, 85   |
Table 6. Sequential re-use of SGIPd (scope of amines).

| Run | amines          | Yield (%) | Run | amines          | Yield (%) |
|-----|----------------|-----------|-----|----------------|-----------|
| 1   | EtNH, 2b       | 3ab, 98   | 5   | cHexNH, 2f     | 3af, 93   |
| 2   | iPrNH, 2c      | 3ac, 97   | 6   |                |           |
| 3   | pyrrolidine, 2d| 3ad, 95   | 7   |                |           |
| 4   | piperidine, 2e | 3ae, 96   |      |                |           |

Scheme 2. Buchwald-Hartwig amination between 4-chloroanisole (4a) and morpholine (2a).

That is to say, the aryne was formed under the strongly basic conditions at a high temperature, and the amines then attacked the aryne intermediate. In contrast, under continuous microwave irradiation conditions at a lower temperature, Buchwald–Hartwig amination might have been selectively activated due to the specific activation of the polar chemical species, Ar–Pd–Br (M2).

Table 7. Optimization of reaction conditions for the reaction of aryl chloride.

| Entry | 1st step | Temp. (°C) | 3aa | 3aa' |
|-------|----------|------------|-----|------|
| 1     |          |            | 59  | ND   |
| 2     |          | 100        | 75  | trace|
| 3     |          | 130        | 78  | 5    |
Table 8. Substrate scope of aryl chlorides and amines

| Entry | Ar–Cl   | amines   | Yield (%) | Entry | Ar–Cl   | amines   | Yield (%) |
|-------|---------|----------|-----------|-------|---------|----------|-----------|
| 1     | 3ea     | 86       |           | 5     | 2i      | 82       |           |
| 2     | 3ai     | 83       |           | 6     | 2j      | 83       |           |
| 3     | 3aj     | 85       |           | 7     | 2f      | 80       |           |
| 4     | 3ef     | 81       |           |       |         |          |           |

ND = Not detected. N = 4-morphorinyl.

Figure 1. Plausible mechanism and effect of microwave irradiation.
Conclusion

In summary, we have developed a product selective Buchwald–Hartwig amination controlled by the combination of the palladium nanoparticle, continuous microwave irradiation, and a co-existing metal solid. In conventional heating, the arylamine formation occurred, and generated the undesired regioisomer due to the high temperature and strongly basic conditions. On the other hand, the Buchwald–Hartwig amination could proceed selectively to obtained the corresponding coupled product by this methodology because the microwave-assisted heating system suppressed the reaction temperature and might have been selectively activated the species with a dipole moment. The Buchwald–Hartwig amination of aryl chlorides, which are inert compound, was also promoted by the microwave-assisted system. Moreover, we found that the SGIPd can be used repeatedly over 10 times for the reaction, and the amount of Pd leached into the reaction mixture was detected at a quite low level (ppb level) by ICP-MS.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chemoselectivity • heterogenous catalyst • microwave • co-existing metal

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In our previous work, it was considered that a minute local hot spot is generated between the aluminum foil and Pt NPs. Therefore, the Suzuki–Miayura coupling of aryl chlorides is promoted.

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