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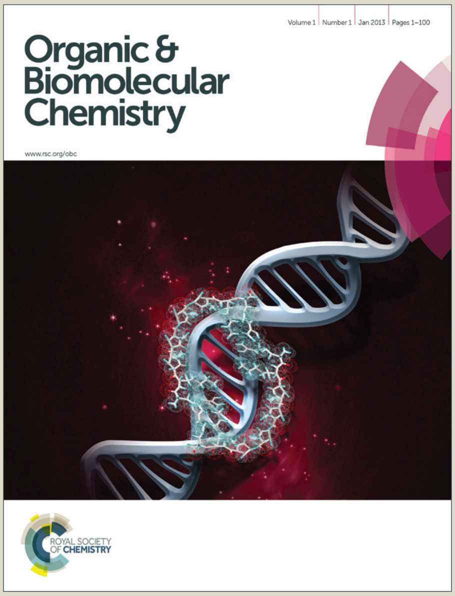

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PAPER

A highly efficient catalyst of nitrogen-based ligand for the Suzuki coupling reaction at room temperature under air in neat water

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Glycine, as a kind of commercially available and inexpensive ligand, is used to prepare an air-stable and water-soluble catalyst used in Suzuki-Miyaura reaction in our study. In the presence of 0.1% [$PdCl_2(NH_2CH_2COOH)_2$] as catalyst, extremely excellent catalytic activity towards the Suzuki-Miyaura coupling of aryl halides containing carboxyl group with various aryl boronic acids is observed at room temperature under air in neat water.

Introduction

The compounds of biphenyl carboxylic acids, such as pharmaceutical intermediate (3-phenyl benzoic acid[1]), monomers (4,4'-biphenyl dicarboxylic acid and 2,5-biphenyl dicarboxylic acid[2]) of polymer materials, key intermediate (4'-hydroxy-4-biphenyl carboxylic acid[3]) of liquid crystal compounds, even the active pharmaceutical ingredient (diflunisal[4]), have high value and play a fairly important role in the field of medicine, organic synthesis, petrochemical industry, materials chemistry and so on. For example, 4-biphenyl carboxylic acid, it is widely used as polarographic analysis regent and organic synthesis intermediate. The economic value is considerable. However, these compounds are usually synthesized through aromatization,[5] Friedel-Crafts acylation,[6] Baeyer-Villiger rearrangement,[7] oxidation, hydrolysis, Kolbe-Schmitt reaction[8] and so on from the ingredient aromatic amines, which appears quite complicate and difficult for synthesis. To our delight, an absolutely novel synthesis method, Suzuki-Miyaura[9] cross-coupling reaction brings great convenience for C-C cross-coupling reactions, but it often performs in organic solvents[10] or under the condition of heating[11] and most catalysts are sensitive to air or water.[12] This oxygen or water sensitivity of catalyst is one of the crucial limitations that hamper the development of practical biaryl synthesis. Therefore, air- and moisture-stable ligands which are easily prepared from commercially available and inexpensive starting materials, are needed for the improvement of Pd-catalyzed cross-coupling reaction. Thus, to seek a cheaper and greener catalyst becomes more significant and challenging .

As we all know, water, as a nontoxic and green solvent for many homogeneously catalyzed reactions，is not only because of its low cost, environmental benefits and safety, but most important is its replacement of organic solvents[13] which are volatile, flammable and toxic. The use of neat water as solvent for Suzuki-Miyaura cross-coupling reaction for synthesizing biaryls which are important units easily found in natural products, pharmaceutical ingredients, functional materials,[14] goes back to Casalnuovo and Calabrese in 1990 and it is the first example about using water in this reaction.[15] Up to present, there has been various methods for the reaction, such as microwave-heating,[16] water-soluble catalysts,[17] MOF,[18] or Pd-nanoparticles,[19] N-heterocyclic carbenes,[20] ligand-free catalytic systems.[21] As we have known, most phosphine ligands are sensitive to air and moisture under homogeneous conditions. So, employment of inexpensive, air- and moisture-stable nitrogen-based ligands for palladium catalysts has attracted increasing attention. A series of nitrogen-based ligands such as 4,4'-azopyridine,[22] NHC-Pd polymer,[23] 1-[N,N',N"-trimethyl-(4-butyl)ammonium]-2-(2-pyridyl)imidazole chloride,[24] have been applied into Suzuki-Miyaura cross-coupling reactions in the neat water. It is possible to perform the reaction using simple palladium salts such as $PdCl_2$ or $Pd(OAc)_2$ under air in neat water.[25] For instance, Monteiro and co-workers[26] showed that the reaction of aryl boronic acids with water-soluble aryl halides can be performed at room temperature in the presence of the palladium salt.

Taking solubility, stability, safety into consideration and from an economic and environmental viewpoint, recently we selected glycine as water-soluble nitrogen-based ligand to synthesize catalyst with palladium chloride. According to reports in the literature, the complex, [$PdCl_2(NH_2CH_2COOH)_2$], has been already synthesized. However, the complex has not been used in Suzuki-Miyaura reaction up to now so that we decide to synthesize the complex and use it as catalyst to catalyze Suzuki-Miyaura cross-coupling reaction. To our delight, it showed highly catalytic activity in the Suzuki-

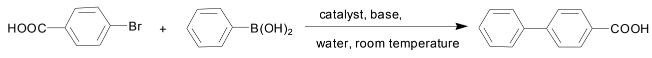
Miyaura coupling reaction of aryl bromides containing carboxyl or phenol group in high yields in water at room temperature under air and aryl chlorides containing carboxyl or phenol group in moderate yields in water without using any additive such as phase-transfer catalysts[27,28]under the condition of heating.

The ligands with nitrogen-based frameworks such as N-heterocyclic carbenes,[29-33] nitrogenacyclic carbenes,[34] cyclometalated imine,[35] diazabutadiene,[36] and guanidines[37] have been reported. Despite the achievements of modest to high yields of products, the systems still require high reaction temperatures in organic solvents under an inert atmosphere. In our studies, [$PdCl_2(NH_2CH_2COOH)_2$], as a catalyst to catalyze Suzuki-Miyaura coupling reaction, has several advantages compared with those reported. Firstly, the ligand of the catalyst is glycine which possesses lots of properties, such as solubility, stability and safety. Because of the properties of the ligand, the catalyst is also water-soluble, stable and safe, which provides the possibility of catalyzing Suzuki-Miyaura coupling reaction in water under air. Secondly, synthesis of the catalyst is extremely simple and it is obtained only by stirring glycine with palladium chloride ($PdCl_2$) in ethanol and acetic acid for 24 hours at room temperature under air. Thirdly, from an economic point of view, glycine is commercially available and inexpensive, which creates feasible condition for industrial production. Finally, the catalyst shows high efficiency to Suzuki-Miyaura coupling reaction at room temperature in water under air with low catalyst loadings.

Results and discussion

Optimization of the coupling reaction conditions

Table 1 Optimization of the reaction conditions



Entry	Catalyst (mol%)	Base (3.0mmol)	Time (h)	Yield (%)
1	0.05	K_2CO_3	0.5	56
2	0.1	K_2CO_3	0.5	82
3	0.5	K_2CO_3	0.5	83
4	1.0	K_2CO_3	0.5	85
5	0.1	K_2CO_3	1.5	89
6	0.1	K_2CO_3	2.5	89
7	0.1	$NaHCO_3$	1.5	65
8	0.1	KOH	1.5	52
9	0.1	K_3PO_4	1.5	27
10	0.1	NaOAc	1.5	17
11	0.1	NEt_3	1.5	trace

Reaction condition: 4-bromobenzoic acid (1.0mmol), phenyl boronic acid (1.2mmol), H_2O(5.0mL), room temperature, air.

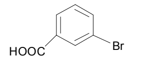
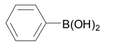
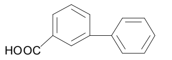
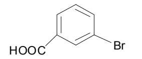
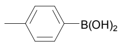
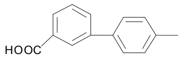
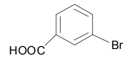
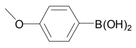
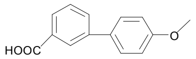
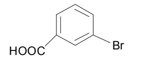
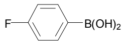
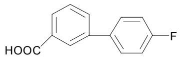
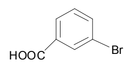
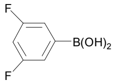
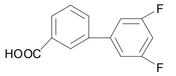
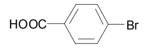
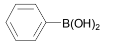
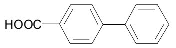
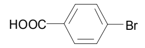
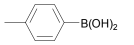
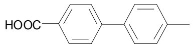
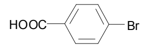
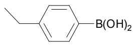
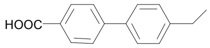
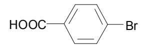
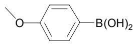
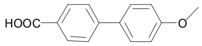
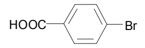
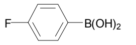
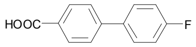
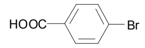
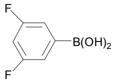
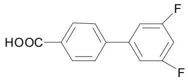
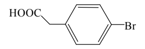
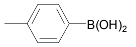
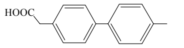
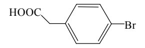
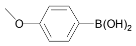
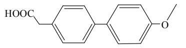
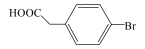
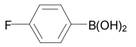
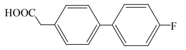
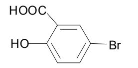
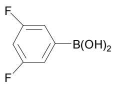
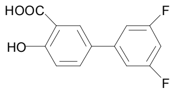
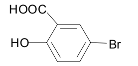
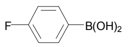
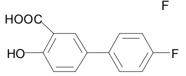
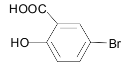
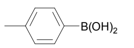
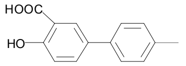
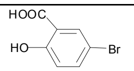
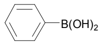
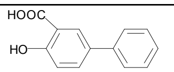
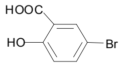
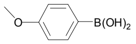
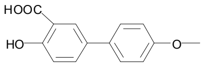
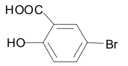
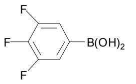
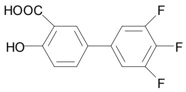
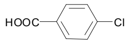
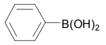
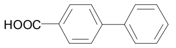
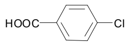
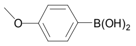
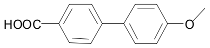
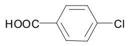
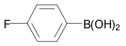
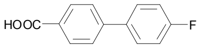
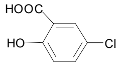
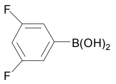
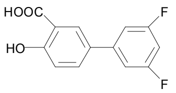
Initially, high yield (Table 1, entry 6) was observed when 4-bromobenzoic acid and phenylboronic acid were selected to test the activity of the catalyst in neat water at room temperature under aerobic conditions for 2.5h. Thus, the two compounds were chosen to establish model reaction for the optimization of our protocol. Results of this preliminary survey were shown in Table 1. As shown in Table 1, when the effect of the amount of the catalyst on the coupling reaction was studied, from the results, we could see that lowering the amount of Pd from 1% mmol to 0.1% mmol did not affect the reaction performance (Table 1, entry 1-4), and the coupling reaction could also be completely finished in excellent yield in 1.5h. Next, we found that reaction time was also an important role on the coupling reaction. Prolonging the reaction time from 0.5h to 1.5h (Table 1, entry 2,5), the yield increased remarkably. However, continuing to prolong time from 1.5h to 2.5h (Table 1, entry 5-6), the yield hardly went on increasing. To further optimize the reaction condition, with the amount of catalyst fixed as 0.1% mol, the reaction proceeded well when inorganic base K_2CO_3 was used, affording the desired coupling product in excellent yield (Table 1, entry 5). Additionally, $NaHCO_3$ and KOH used in this reaction gave moderate yield (Table 1, entry 7-8). In contrast, K_3PO_4 or NaOAc slightly promote the reaction (Table 1, entry 9-10) and organic base (NEt_3) scarcely promote the reaction (Table 1, entry 11).

Scope and limitations of the substrates

To further investigate the scope and limitations of this methodology, we carried out different aryl halides coupling with various aryl boronic acids under optimized conditions. As shown in Table 2, the coupling of 3-bromobenzoic acid or 4-bromobenzoic acid with phenyl boronic acid, 4-methylphenyl boronic acid, 4-fluorophenyl boronic acid and 4-methoxyphenyl boronic acid gave products in high yield from 89% to 99% with 0.1% mmol catalyst at room temperature under air in neat water after 1.5 h (Table 2, entry 1-4 and 6-10), showing high efficiency and good selectivity. Using 4-bromophenylacetic acid instead of 3-bromobenzoic acid or 4-bromobenzoic acid, the cross-coupling reaction was completed in high yield from 87% to 96% with 0.1% mmol catalyst at room temperature under air in neat water after 6 h (Table 2, entry 12-14). Additionally, 5-bromosalicylic acid containing an electron-donating group (-OH) could also couple with various aryl boronic acids in high yield (Table 2, entry 15-19), but it needed longer reaction time(6h) and higher amount of catalyst (1% mmol). Besides, it was worth noting that a weaker base ($NaHCO_3$) was more suitable for the coupling of 5-bromosalicylic acid with phenyl boronic acid, 4-methoxyphenyl boronic acid and 3,4,5-trifluoro phenyl boronic acid than K_2CO_3 used. However, comparatively low yield (Table 2, entry 5, 11, 20) was obtained when 3-bromobenzoic acid or 4-bromobenzoic acid coupling with 3,5-difluorophenyl boronic acid or 3,4,5-trifluoro phenyl boronic acid even in the presence of 1% mol catalyst for 6h, which demonstrated that reactivity of the coupling reaction decreased sharply when aryl boronic acids containing more than one strongly electron withdrawing group. ON the other hand, aryl bromides containing carboxyl group bearing different electrical groups also had a significant effect on the coupling reaction. From Table 2, there were clear differences among 3-bromobenzoic acid, 4-bromobenzoic acid, 4-bromophenylacetic acid and 5-bromosalicylic acid. Obviously, 4-bromophenylacetic acid containing a weak electron withdrawing group (-CH_2COOH) or 5-bromosalicylic acid bearing strongly electron-donating group (-OH) needed longer reaction time or higher amount of catalyst than 3-bromobenzoic acid and 4-bromobenzoic acid. This is probably due to the binding of such substrates to the metal center, resulting in the formation of inactive substrate-metal complexes.[38] For aryl chlorines containing carboxyl group, it was much difficult to coupling with aryl boronic acids even under the condition of heating, prolonging reaction time (Table 2, entry 21-24).

Table 2 Suzuki–Miyaura reaction under optimized conditions

$$Ar_1-Br \;+\; Ar_2-B(OH)_2 \xrightarrow[\text{water (5.0 mL)}\\ \text{rt, 1.5h}]{\text{catalyst(0.1\%),}\\ K_2CO_3\text{ (3.0mmol)}} Ar_1-Ar_2$$

Entry	Aryl halides	Aryl boronic acids	Products	Yield[a] (%)
1				97
2				96
3				98
4				99
5				56
6				89
7				91
8				91
9				99
10				93
11				67[c]
12				92[b]
13				92[b]
14				96[b]
15				93[c]
16				91[c]
17				99[c]
18				91[d]
19				99[d]
20				77[e]
21				80[f]
22				73[f]
23				75[f]
24				55[f]

Reaction condition: Carried out with aryl bromide (1.0 mmol), aryl boronic acid (1.2 mmol), catalyst (0.1% mol), K_2CO_3 (3.0 mmol), H_2O (5.0mL) at room temperature under air for 1.5h. [a] Isolate yield was based on aryl halides. [b] Carried out with catalyst (0.1% mmol) in 6h. [c] Carried out with catalyst (1% mmol) in 6h. [d] Carried out with $NaHCO_3$(3.0mmol) and catalyst (1% mmol) in 6h. [e] Carried out with $NaHCO_3$(3.0mmol) and catalyst (1% mmol) in 20h. [f] Carried out with KOH(3.0mmol) and catalyst (3%mol) in 20h under 100□.

Experimental section

Reagents and machine

All reagents employed in the reaction were analytical grade, obtained commercially from Aladdin or Alfa Aesar and used without further purification. ^{1}H NMR spectra was recorded on a Bruker Avance III (400MHz) spectrometer using tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. Elemental analyses (C, H, N) were carried out on a Perkin Elmer model 240 C automatic instrument. Electrospray mass spectra (ES-MS) were recorded on a Finnigan LCQ mass spectrometer.

Synthesis of the catalyst

A mixture of glycine(10.2mmol), palladium chloride (5.0mmol), ethanol (30mL) and acetic acid (5mL) was stirred at room temperature under air for 24h in a round-bottomed flask. After 24h, large amounts of light brown precipitate emerged in the solution. Then, the precipitate was filtered and washed with cool ethanol. Lastly, a light brown compound was obtained after dried by vacuum. On the basis of elemental analysis, the complex was found to have the composition of C (14.90%), H (3.10%), N (8.56%); ESI-MS(m/z): 326.8[M+1]. Yield: 0.93g, 57%.

$$PdCl_2 + 2NH_2CH_2COOH \xrightarrow[\text{rt, 24h}]{\text{ethanol}\\ \text{acetic acid}} PdCl_2(NH_2CH_2COOH)_2$$

Fig. 1 Synthesis of catalyst

Typical experimental procedure for Suzuki coupling of aryl halides and aryl boronic acids

A mixture of aryl halides (1.0 mmol), aryl boronic acid (1.2 mmol), catalyst (0.1% mmol), K_2CO_3 (3.0mmol), distilled water (5.0 mL) was stirred at room temperature under air for 1.5h in a round-bottomed flask. After 1.5h, the precipitate in the mixture was filtered and washed with distilled water so that the product was separated from the mixture. Then, the precipitate was dissolved in boiling water (100 mL) for 10 min and filtered immediately under decompression to remove the by-product deriving from homo-coupling of aryl boronic acids. Next, the solution was acidized with dilute hydrochloric acid under stirring for 0.5h until the PH was up to 3~4 so that the precipitate would formed completely. Following, the white precipitate was filtered under decompression again and washed with 20mL distilled water. After that, the white solid was dissolved in 10mL ethyl acetate and two tablespoons of desiccant (Na_2SO_4 or $MgSO_4$) were added into the ethyl acetate to get rid of water from product. Finally, the solution was filtered and evaporated under vacuum, leaving the product, which is confirmed by ^{1}HNMR Spectroscopy.

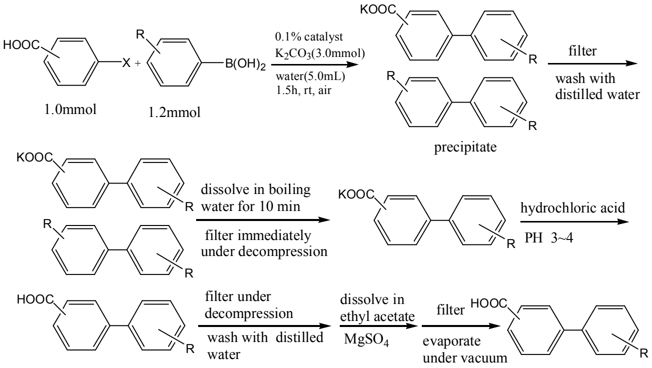


Fig. 2 experimental procedure

Conclusions

We have shown that the complex ($[PdCl_2(NH_2CH_2COOH)_2]$) as a catalyst with small amount can be used to catalyze the Suzuki–Miyaura coupling reaction of aryl bromides containing carboxyl group with varieties of aryl boronic acids conveniently at room temperature under air in neat water, which gives an extremely fast, highly efficient and much more green approach to obtain biphenyl carboxylic acids (such as pharmaceutical intermediates, monomers of polymer materials, key intermediate of liquid crystal compounds) that play a fairly significant role in the field of medicine, organic synthesis, materials chemistry. Thus, the method shows considerable applied and economic value because of its extremely mild conditions with good functional group tolerance and excellent yield.

Notes and references

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