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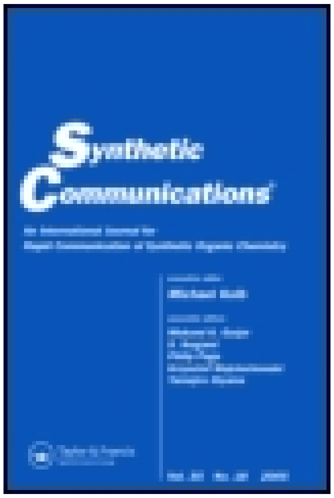

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A Simple and Efficient Palladium Catalyst of Nitrogen-Based Ligand for Cu(I)- and Amine- Free Sonogashira Reaction

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A Simple and Efficient Palladium Catalyst of Nitrogen-based Ligand for Cu(I)- and Amine- Free Sonogashira Reaction

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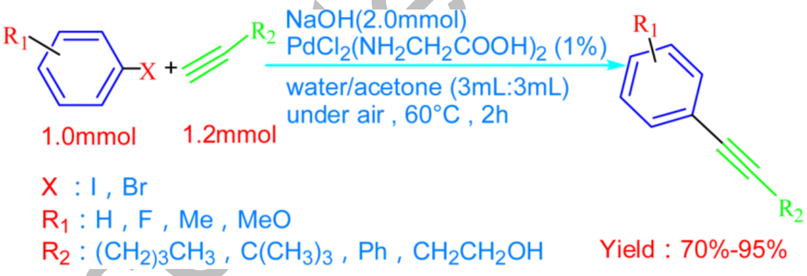
Abstract

Glycine, as a kind of commercially available and inexpensive ligand, is used to prepare an air-stable and water-soluble catalyst used in Sonogashira reaction in our study. In the presence of 1% [$PdCl_2(NH_2CH_2COOH)_2$] as catalyst, excellent catalytic activity towards the Sonogashira coupling of aryl iodides with terminal alkynes without using any additive such as Cu(I)-cocatalyst is observed in a mixture of water and acetone (3mL:3mL) under air at 60°C with NaOH as a base, giving products in good to excellent yields.



KEYWORDS: Catalysis; palladium complex; Sonogashira reaction; strategy

INTRODUCTION

The synthesis of alkynyl compounds has attracted considerable interest because of their appearance in many biologically active natural products (such as panaxynol, panaxydol, panaxytriol showing certain anti-cancer effects[1]) and being as key intermediates of pharmaceuticals or drug-like molecules[2–3] and even being as monomers of polymer materials[4–5], liquid crystal material[6–7], showing great application perspective and considerable economic value in the field of medicine, organic synthesis and materials chemistry. Thus, much attention has been focused on the development of efficient and selective methods for the synthesis of alkynes.

Easily, transition-metal-catalyzed cross-coupling reactions can be considered as cornerstones in organic synthesis for the formation of carbon-carbon bonds. In these reactions, the coupling of aryl or alkenyl halides with terminal alkynes catalyzed by palladium in the presence of Cu(I) co-catalyst or not, commonly known as Sonogashira cross-coupling reaction, is one of the most powerful methods for straightforward sp^2-sp carbon-carbon bond formation reaction to prepare arylalkynes and conjugated enynes encountered frequently in natural products[8–9], bioactive molecules[10–11], molecular electronics[12–13], dendrimeric and polymeric materials[14–15]. Therefore, considerable effort has been directed to the development of new and efficient palladium catalytic systems for Sonogashira cross-coupling reaction[16–21]. Generally, the Sonogashira reaction is performed with palladium-phosphane ligand complex, such as $Pd(PPh_3)_2Cl_2$, $Pd(dppe)Cl_2$ and $Pd(dppf)Cl_2$, in the presence of Cu(I) salt as co-catalyst and an amine as a solvent, such as triethylamine under homogeneous conditions. But when these palladium species are employed, it often requires high loading of palladium (usually up to

5 mol %) and a larger amount of the Cu(I) salt. Additionally, many phosphine ligands are air-sensitive and not environmentally friendly, significantly limiting their synthetic applications[22–23]. Besides, the presence of Cu(I) salt can result in the formation of oxidative homocoupling reaction of alkynes[24]. In the past decades, although significant developments from the original palladium-phosphorus complexes[25] to palladium-P,N or palladium-P,O complexes[26], palladium-nitrogen complexes[27]and N-Heterocyclic Carbene palladium complexes[28], palladacycle patalysts[29], even the use of ligand-free palladium catalysts[30], have been achieved towards the Sonogashira reaction with moderate to high yields[31–34], most systems still require high reaction temperatures in organic solvents under an inert atmosphere and even need the presence of Cu(I) salt and an amine as solvent. Therefore, to explore a more active catalyst for simpler, milder and more effective reaction conditions with the Cu(I)-, amine- and phosphine-free catalytic system becomes more significant and challenging for chemistry researchers.

Taking stability and safety into consideration and from an economic and environmental viewpoint, recently we selected glycine as water-soluble nitrogen-based ligand to synthesize a catalyst with palladium chloride and found that glycine was a highly efficient ligand for the palladium catalyzed Suzuki–Miyaura cross-coupling reaction giving excellent yields for aryl bromides and moderate for aryl chlorides[35–36] so that we expected to extend the use of this catalyst to other palladium-catalyzed transformations. In this paper, we report a highly efficient [$PdCl_2(NH_2CH_2COOH)_2$]-catalyzed Sonogashira cross-coupling reaction of aryl halides with terminal alkynes to form internal alkynes. In our studies, [$PdCl_2(NH_2CH_2COOH)_2$], as a catalyst for the Sonogashira coupling reaction, has several advantages compared with those reported[37–39]. 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 Sonogashira reaction in water under air. Secondly, synthesis of the catalyst is extremely easy 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 Sonogashira reaction in a mixture of water and acetone (3mL:3mL) under air at 60°C with 1% catalyst and NaOH as a base in 2 hours with the Cu-, amine- and phosphine-free catalytic system, giving products in moderate to good yields.

RESULTS AND DISCUSSION

Optimization Of The Coupling Reaction Conditions

Initially, moderate yield (Table 1, entry 1-2) was observed when iodobenzene and phenyl acetylene were selected to test the activity of the catalyst in a mixture of water and ethanol or PEG-400 under air at 60°C with NaOH (2.0mmol) as a base for 2h. Thus, the two compounds were chosen to establish guidelines for the optimization of our protocol as the model reaction. Because of good solubility of the catalyst in water, we continued to explore solvent system consisted of water and another organic solvent. As shown in Table 1, when 1,4-dioxane or THF was selected to be as mix solvent with water (Table 1, entry 3-4), low yield was observed. However, relatively high yield (Table 1, entry 5) was observed when acetone was chosen as solvent with water in the proportion of 3mL:3mL. Next, different proportions of acetone and water were studied but the reaction was not performed well under other proportions (Table 1, entry 6-9) so that the mix solvent of water and acetone(3mL:3mL) was found to be the best reaction solvent.

After the best reaction solvent was found, other reaction conditions, such as reaction temperature or time, were studied in detail. Results of this preliminary survey are shown in Table 2. As shown in Table 2, 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 2% mol to 1% mol did not affect the reaction performance (Table 2, entry 4-5). When the amount of the catalyst was reduced to 0.5%, it gave products in moderate yield(Table 2, entry 3) and When being reduced to 0.1%, the coupling reaction could hardly be performed (Table 2, entry 1-2). So, 1% mol catalyst was optimal for the system. Next, we found that reaction temperature had also an important role on the coupling reaction. Increasing the reaction temperature from 30℃ to 60℃ (Table 2, entry 6-8), the yield also increased remarkably. It was worth noting that low yield (34%) was obtained when reaction temperature was up to 80℃ (Table 2, entry 9), indicating that high temperature was not suitable for the proceeding of the reaction under this system. In addition, prolonging the reaction time from 0.5h to 2h (Table 2, entry 10-12), the yield increased from 86% to 93%. To further optimize the reaction condition, with the amount of catalyst fixed as 1% mol, the reaction proceeded well when inorganic base NaOH was used, affording the desired coupling product in excellent yield (Table 2, entry 12) under air at 60°C for 2h. However, NEt_3 and K_3PO_4 used in this reaction gave moderate yield

(Table 2, entry 13-14). In contrast, K_2CO_3 and Pyridine slightly promoted the reaction (Table 2, entry 15-16) and organic base 1,2-propanediamine scarcely promoted the reaction (Table 2, entry 17).

Scope And Limitations Of The Substrates

To further investigate the scope and limitations of this methodology, we carried out cross-couplings of different aryl halides including electron-neutral, electron-rich and electron-poor aryl iodides with various terminal alkynes under optimized conditions. As shown in Table 3, although all the aryl iodides could couple smoothly with various terminal alkynes under the optimized reaction condition, aryl iodides with electron-donating groups such as 4-iodoanisole (Table 3, entry 12-15), gave moderate yields (70-79%) in 2 hours, showing slightly low reactivity. In contrast, aryl iodides with electron-withdrawing groups such as 4-fluoroiodobenzene (Table 3, entry 9-11), gave good yields (78%-88%) under the same reaction condition, showing slightly high reactivity. Additionally, electron-neutral aryl iodides such as iodobenzene or 4-iodotoluene coupling with terminal alkynes also gave desired products in moderate to good yields (Table 3, entry 1-8). On the other hand, the terminal alkynes also have a significant effect on the coupling reaction. As shown in Table 3, the reaction of phenylacetylene, 1-hexyne, 3-butyn-1-ol with aryl halides gave the superior yields of the products to 3,3-dimethyl-1-butyne, indicating that terminal alkynes with steric hindrance, such as 3,3-dimethyl-1-butyne, gave products in moderate yields, significantly being lower than the 1-hexyne or 3-butyn-1-ol without steric hindrance. Moreover, the relatively low activity was obtained when aryl bromides coupling with various terminal alkynes.

Possible Mechanism Of The Catalyst For Sonogashira Reaction

The mechanism of the copper-free Sonogashira reaction is still not well-known. The possible mechanism is as follow. The first step would be the oxidative addition of aryl halides to the palladium(0) complex. However, the second step is under debate. The base employed is usually hard to deprotonate the alkyne for the reaction with the oxidative addition palladium(0) complex(*trans*-R_1PdXL_2) so that complexation of the alkyne to the complex is supposed to proceed first with displacement of one ligand to give intermediate complex(RCCH)-$PdXL_2$. The ligated alkyne would be more easily deprotonated by base such as NaOH used in the reaction, forming the new complex R_1Pd-$(CCR_2)L_2$, which gives the coupling product R_1-CC-R_2 by reductive elimination.

Reagents And Machines

All reagents employed in the reaction were analytical grade, obtained commercially from J&K China Chemical ltd and used without further purification. ^1H and ^{13}C 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, 0.765g), palladium chloride (5.0mmol,0.886g), 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 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%.

Recovery And Recycling Of The Catalyst

The palladium catalyst can be easily recovered by simple extraction. Because the catalyst is water-soluble and reaction solvent is consisted of water and acetone so that the catalyst can be separated from products and recovered by simple extraction. In addition, The catalyst used in the reaction is recyclable really. But the catalytic efficiency is decreasing gradually with recyclable time increasing from 93% initially to 53% lastly. From Table 4, the recycling of catalyst was investigated using iodobenzene and phenyl acetylene as model substrates. We can see that the efficiency of catalyst' recycling decreasing apparently, even prolonging the reaction time.

General Procedure For The Synthesis

The aryl halides (1.0 mmol), terminal alkynes (1.2 mmol), catalyst (1% mol, 0.003268g), NaOH (2.0 mmol, 0.08g), water/acetone (3mL:3mL) were added to a flask and stirred under air at 60°C for 2 hours. Then, the 5mL brine was added to quench the reaction and the mixture was extracted with ethyl acetate (3×15 ml). The combined organic phase was dried with Na_2SO_4 for 3 hours. Next, the organic phase was filtrated and removed on a rotary evaporator. Finally, the products was isolated by thin layer chromatography and the purified products were identified by ^1H and ^{13}C NMR.

CONCLUSION

In summary, in the present letter it has been shown that the use of $[PdCl_2(NH_2CH_2COOH)_2]$ as catalysts in a mixture of water and acetone (3mL:3mL) under air at 60°C with NaOH as a base is a very convenient way to carry out Sonogashira coupling reaction with the Co-, amine- and phosphine-free catalytic system, which gives an extremely fast, highly efficient and much more green approach to obtain alkynyl compounds found easily in natural products, bioactive molecules, dendrimeric and polymeric materials, demonstrating great industrial application perspective and considerable economic value in the field of medicine, organic synthesis and material chemistry.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher’s website.

REFERENCES

1. Kim, J.Y.; Lee, K.W.; King, S.H. *Planta Med*. **2002**, *68(2)*, 119.

2. Barry, M.T.; Zachary, T.B. *J. Am. Chem. Soc*., **2004**, *126(43)*, 13942.

3. Binh, G.V.; Kim,S.H; Abraham,S.; Theodorakis, E.A. *Angew. Chem. Int. Ed*., **2004**, *43(30)*, 3947.

4. Li, J.-Z.; Ambroise, A.; Lindsey, J.S. *J. Am. Chem. Soc*., 1999, *121(38)*, 8927.

5. Strachan, J.P.; Gentemann, S.; Seth, J. *Inorg. Chem*. **1998**, *37,* 1191.

6. Jacky W. Y. L. and Tang,B.Z. *Acc Chem Res*. **2005**, *38(9)*, 745-754.

7. Liu, J.Z.; Jacky, W. Y. L. and Tang, B.Z. *Chem Rev*., **2009**, *109(11)*, 5799 .

8. Robert D. M. D. and Marquez, R. Angew. *Chem. Int. Ed.* **2001**, *40(3)*, 603.

9. Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65(21)*, 7110.

10. Gary, A.; Hügel, H. M.; Nurlawis F. *Synlett.* **2002**, *3*, 495.

11. Tehrani, L.; Roppe, J.; Schweiger, E. J.Med. Chem. **2003**, *46(2)*, 204.

12. Mongin, O.; Moreaux, L.; Mertz, *J. Org. Lett*. **2002**, *4(5)*, 719.

13. Wong, K.-T.; Chun, C. H. *Org. Lett*. **2001**, *3(2)*, 173.

14 . Wagner, R. W.; Kim, D.; Bocian, D. F. *J. Org. Chem*., **1998**, *63(15)*, 5042.

15. Strachan, J.-P.; Gentemann, S.; Seth, J.; Kalsbeck, W. A.; Lindsey, J. S.; Holten, D.; Bocian, D. F. *Inorg. Chem.*, **1998**, *37*, 1191.

16. Arques, A; Auñon, D.; Molina, P. *Tetrahedron Lett.*, **2004**, *45(22)*, 4337.

17. Cheng, J.; Sun, Y.-H.; Wang, F. *J. Org. Chem.*, **2004**, *69(16)*, 5428.

18. Wolf, C.; Lerebours, R. *Org. Biomol. Chem.*, **2004**, *(2)*, 2161.

19. Méry, D.; Heuzé, K.; Astruc, D. *Chem. Commun.*, **2003**, *(15)*, 1934.

20. Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.*, **1993**, *34(40)*, 6403.

21. Heidenreich, R. G.; Klaus,K.; Krauter J. G. E. *Synlett.* **2002**, *(7)*,1118.

22. Matthew, R. N.; Gregory, C. F. *Org. Lett*., **2001**, *3(26)*, 4295.

23. Gelman, D; Buchwald, S.L. *Angew. Chem. Int. Ed*., **2003**, *42(48)*,5993.

24. Siemsen, P; Livingston R. C.; Diederich, F. *Angew. Chem. Int. Ed*. **2000**, *39(15)*, 2632.

25. Heuzé, K.; Méry, D.; Gauss,D. *Chem. Eur.J.*, **2004**, *10(16)*, 3936.

26. Nishide,K.; Liang, H.; Yoshifuji, M. *J. Organomet. Chem*., **2005**, *690*, 4809.

27. Gronnow, M.-J.; Luque,R.; Duncan J.-M. *Green Chem.*, **2005**,*7*, 552.

28. Wolfgang,A.-H. *Angew. Chem. Int. Ed.*, **2002**, *41(8)*, 1290.

29. Beletskaya, I. -P., Cheprakov, A. V. K. *J. Organomet. Chem.*, **2004**, *690(17)*, 4055.

30. Urgaonkar, S.; Verkade, J.-G. *J. Org. Chem.,* **2004**, *69*, 5752.

31. Lin, B.-N.; Huang, S.-H.; Wu, W.-Y. *Molecules*, **2010**, *15*, 9157.

32. Bahman, T.; Fatemeh, F.; Soheila, G. and Hamed, A. *New J.Chem*., **2013**,*37*, 2011.

33. Li, J.-H.; Liang Y. and Xie Y-.X. *J. Org. Chem*., 2005, 70, 4393.

34. Li P.-H.; Wang L.*SYNLETT*, **2006**, *14*,2261.

35. Liu,S.-W.; Guo, M.-P.; Li,X.-G. *Org. Biomol. Chem*., **2014**, *12 (25)*, 4511.

36. Guo, M.-P.; Liu,S.-W.; Zhou,X.-L. *Molecules*, **2014**,*19(5)*, 6524.

37. Elizabeth, T.; Leon, W.; Neil, W. *SYNTHESIS*, **2009**,*5*,829.

38. Sameer U. and John G.-V. *J. Org. Chem.*, **2004**,*69*,5752.

39. Irina, P.-B.; Gennadij V.-L. and Nikolai V.-L. *Tetrahedron Lett.*, **2003**, *44*, 5011.

Table 1. Optimization of the reaction solvent

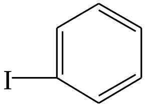
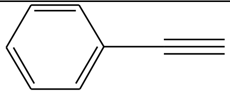
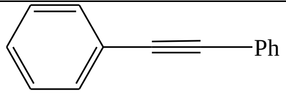
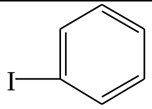
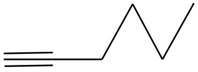
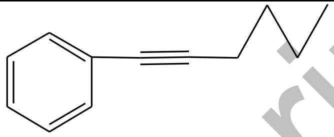
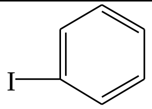
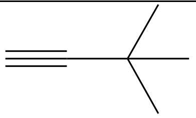
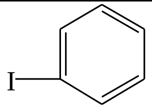
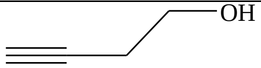
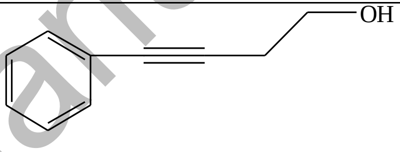
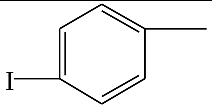
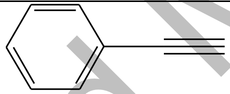
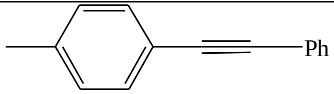
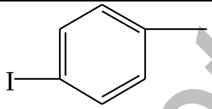
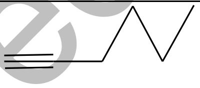
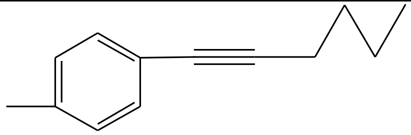
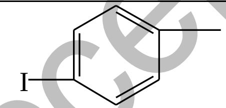
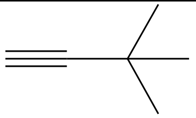
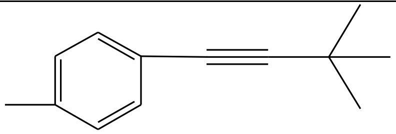
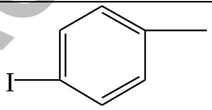
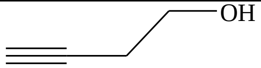
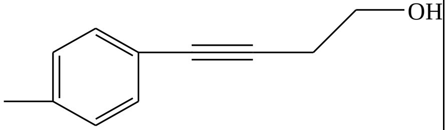
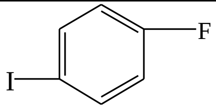
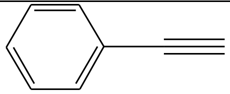
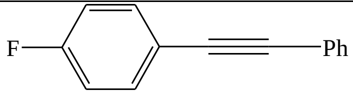
Entry	**water/organic solvent**	**Yield (%)**[a]
1	Water/ethanol(3mL:3mL)	55
2	Water/PEG-400(3mL:3mL)	74
3	Water/THF(3mL:3mL)	44
4	Water/1,4-dioxane(3mL:3mL)	30
5	Water/acetone(3mL:3mL)	93
6	Water/acetone(0mL:6mL)	37
7	Water/acetone(2mL:4mL)	34
8	Water/acetone(4mL:2mL)	48
9	Water/acetone(6mL:0mL)	50

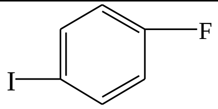
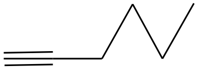
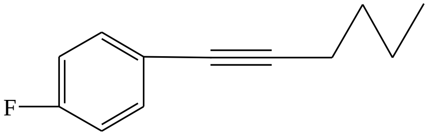
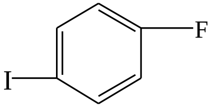
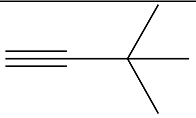
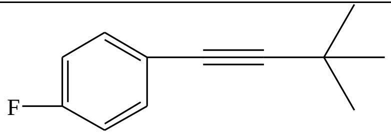
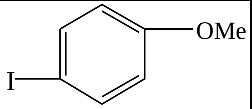
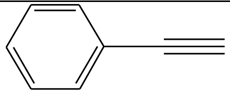
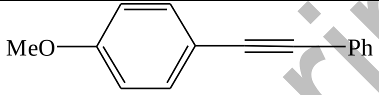
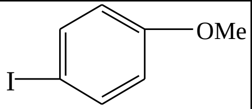
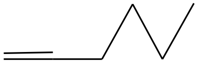
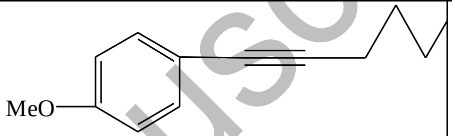
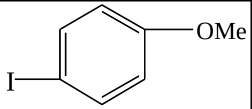
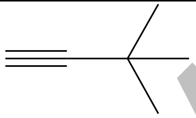
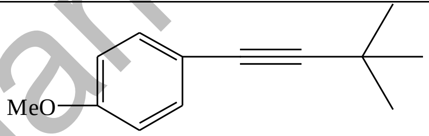
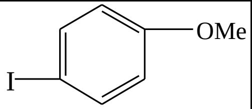
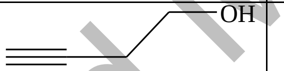
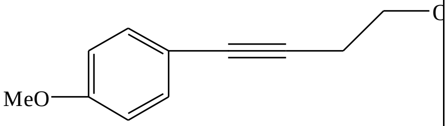
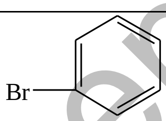
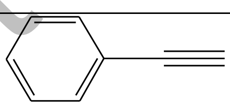
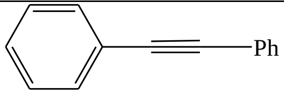
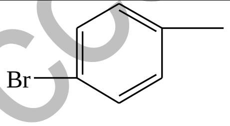
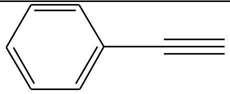
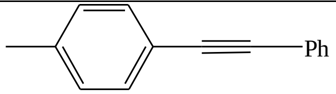
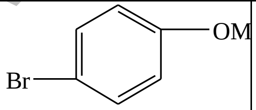
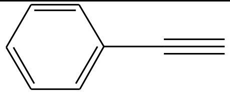
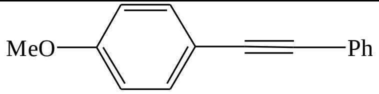
Reaction condition: [a] Isolate yield was based on aryl halides.

Table 2. Optimization of the other reaction conditions

Entry	Catalyst (mol%)	Bases (2.0mmol)	Time (h)	Temperature(℃)	Yield (%)
1	0.05	NaOH	0.5	60	0
2	0.1	NaOH	0.5	60	13
3	0.5	NaOH	0.5	60	75
4	1	NaOH	0.5	60	86
5	2	NaOH	0.5	60	88
6	1	NaOH	0.5	30	44
7	1	NaOH	0.5	45	61
8	1	NaOH	0.5	60	86
9	1	NaOH	0.5	80	34
10	1	NaOH	0.5	60	86
11	1	NaOH	1	60	89
12	1	NaOH	2	60	93
13	1	K_3PO_4	2	60	55
14	1	NEt_3	2	60	56
15	1	K_2CO_3	2	60	15
16	1	pyridine	2	60	11
17	1	1,2-propanediamine	2	60	trace

Table 3. Sonogashira reaction under optimized conditions

Entry	Aryl halides	Terminal alkynes	Products	Yield (%)
01				93
02				87
03				78
04				92
05				85
06				84
07				70
08				95
09	 		 	88

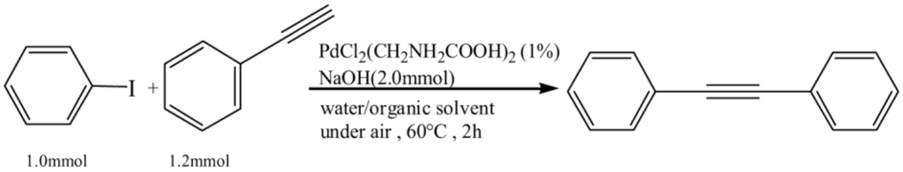
10				85
11				78
12				78
13				79
14				70
15				81
16				50
17				53
18				42

Reaction condition: [a] Isolated yield was based on aryl halides.

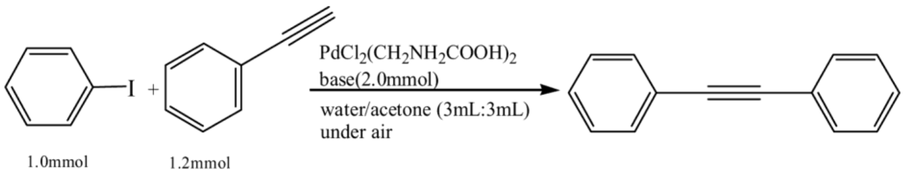
Table 4. Recycling of catalyst for Sonogashira reaction of iodobenzene with phenyl acetylene

Entry	**recycle**	**Time (h)**	**Isolated yield (%)**
1	1	2	93
2	2	2	77
3	3	4	80
4	4	16	53
5	5	24	14

Scheme 1. Optimization of the reaction solvent



Scheme 2. Optimization of other reaction conditions



Scheme 3. Sonogashira reaction under optimized conditions