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Highly Efficient Pd/Tetraphosphine Catalytic System for Copper-Free Sonogashira Reactions of Aryl Bromides with Terminal Alkynes

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Abstract In this study, an easily synthesized polydentate ligand *N,N,N',N'*-tetra(diphenylphosphinomethyl)-1,2-ethylenediamine (1) in combination with $[Pd(C_3H_5)Cl]_2$ was found to be an active catalyst in copper-free Sonogashira reactions. Most substrates, including steric hindered phenyl bromides and heteroaryl bromides, could couple efficiently with terminal alkynes in the presence of low catalyst loading (0.1 mol%) and this catalytic system showed excellent functional group tolerance. The influence of water in this system was also preliminarily investigated via ^{31}P NMR in situ; that is, appropriate water favors the reaction while excess hindered this reaction.

Keywords Palladium · Tetraphosphine · Copper-free · Sonogashira reaction · Aryl bromides

1 Introduction

Palladium-catalyzed Sonogashira cross-coupling of aryl halides with terminal alkynes is among the most powerful and straightforward strategies for the formation of $C(sp^2)$–$C(sp)$ bonds [1–3]. Due to its good functional group tolerance, this reaction has been widely utilized in total synthesis [4] and pharmaceuticals [5]. In the past decades, much effort has been devoted to the design of new ligands and the exploration of catalytic methods, and one of the fields was elimination of copper salt from the reaction [6, 7], as the presence of copper might lead to alkyne dimerization (Glaser coupling) and make the product difficult to isolate [8]. Recently, palladacycles and ionic liquids systems have been applied in the copper-free reactions. C. Nájera and I. Błaszczyk groups utilized palladacycle catalysts in the coupling of iodobenzene and its derivatives [9, 10]. I. Ryu and A. Trzeciak employed $PdCl_2(PPh_3)_2$ and $PdCl_2[P(OPh)_3]_2$ as catalyst precursors and [BMIm][PF_6] as reaction medium for the coupling of aryl iodides [11, 12]. Meanwhile, Hierso et al. [13] reported a [BMIM][BF_4]-$[Pd(C_3H_5)Cl]_2$-dppf system for the coupling of aryl bromides under copper-free condition. Additives (silver or zinc salts) were alternative choice to promote the reaction but might cause the catalytic system more complicated [14–17]. Herein simple copper-free protocols without those salts were published later. However it was noteworthy that high catalyst loading (1–5 mol%) was commonly needed in these methodologies for the active species cannot be fully stabilized by ligands [18–23].

Polydentate phosphines such as *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (Tedicyp) [24] and 1,2-bis(diphenylphosphino)-1′-(diisopropylphosphino)-4-tert-butylferrocene [$Fc(P)_2^tBu(P^iPr)$] [25] were successfully used in Sonogashira reactions to reduce the catalyst loading. Tedicyp in combination with $[Pd(C_3H_5)Cl]_2$ could lower the catalyst loading to 10^{-5} mol% with 4-Trifluoromethylbromobenzene as substrate [26–30], and the use of [$Fc(P)_2^tBu(P^iPr)$] decreased the amount of catalyst to 10^{-4} mol% for the coupling of 4-bromoacetophenone. However, the long synthetic routes of these two ligands may limit their applications, and catalytic amount of CuI (5 mol%) was still required in both systems.

We have recently reported the successful application of a simple tetraphosphine *N,N,N',N'*-tetra(diphenylphosphinomethyl)-1,2-ethylenediamine (1) (Fig. 1) in Heck

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reaction [31]. In this paper we tried to report the efficiency of this structurally simple and easily synthesized ligand for the Sonogashira coupling of aryl bromides with terminal alkynes in the absence of copper (Scheme 1).

2 Results and Discussion

Our work began with the screening of catalyst precursors for the coupling of phenyl bromide with phenylacetylene as the nature of Pd source is critical for the Sonogashira reactions [32]. By monitoring the reaction, $[Pd(C_3H_5)Cl]_2$ was proved to be the most efficient catalyst precursor. In our previous research, it was observed that **1** only played the role of tetradentate phosphine under the reaction condition for ^{31}P NMR spectra of **1** with $[Pd(C_3H_5)Cl]_2$ in situ did not show any evidence to prove the coordination of nitrogen atom with Pd [31]. We next examined the effect of base and solvent on the Sonogashira reaction in the presence of **1**(0.1 mol%)-$[Pd(C_3H_5)Cl]_2$(0.05 mol%). Both polar (DMF and DMA) and apolar solvents (xylene) showed moderate activity, so did the ether solvents (DME and 1,2-diethoxylethane) (Table 1, entries 1–7). It was concluded that moderate polar aprotic solvents in combination with inorganic base was useful [33]. 1,4-dioxane in combination with K_2CO_3 or K_3PO_4 were tested in the reaction, resulting that not only the conversion of phenyl bromide increased, but also high selectivity was observed (Table 1, entries 8, 9). In contrast, neither weak nor strong inorganic bases could fully promote the reaction (Table 1, entries 10–12). Likewise, the associations of 1,4-dioxane to organic bases were less efficient for the reaction (Table 1, entries 13, 14). Increasing the reaction temperature and extending the reaction time, the conversion was up to 96 % in the presence of K_3PO_4 (Table 1, entry 15).

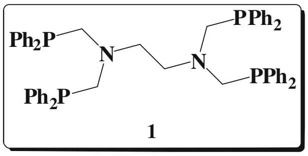


Fig. 1 Ligand 1

Table 1 Screening of solvents and bases in Sonogashira reactions of phenyl bromide with phenylacetylene

Entry	Solvents	Base	Conversion (%)[a]
1	DMF	K_2CO_3	68
2	DMF	K_3PO_4	74
3	DMA	K_2CO_3	54
4	DMA	K_3PO_4	81
5	Xylene	K_3PO_4	60
6	DME	K_3PO_4	72[b]
7	1,2-Diethoxylethane	K_3PO_4	73
8	1,4-Dioxane	K_2CO_3	81
9	1,4-Dioxane	K_3PO_4	84
10	1,4-Dioxane	$NaHCO_3$	6
11	1,4-Dioxane	NaOAc	10
12	1,4-Dioxane	KOH	65
13	1,4-Dioxane	NEt_3	9
14	1,4-Dioxane	DMAP	Trace
15	1,4-Dioxane	K_3PO_4	96[c], 10[d]

Reaction condition: $[Pd(C_3H_5)Cl]_2$ (0.05 mol%), **1** (0.1 mol%), phenyl bromide (1 mmol), phenylacetylene (1.2 *eq.*), base (2 *eq.*), solvent (3 mL), 100 °C, 15 h

[a] Conversions according to GC based on the amount of phenyl bromide used

[b] 85 °C

[c] 105 °C, 20 h

[d] 0.01 mol% of catalyst loading, 105 °C, 20 h

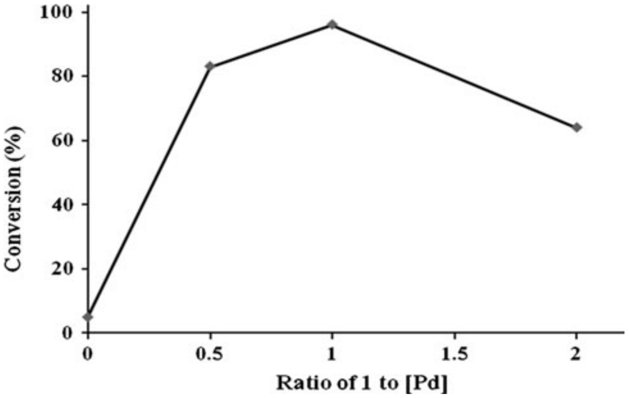
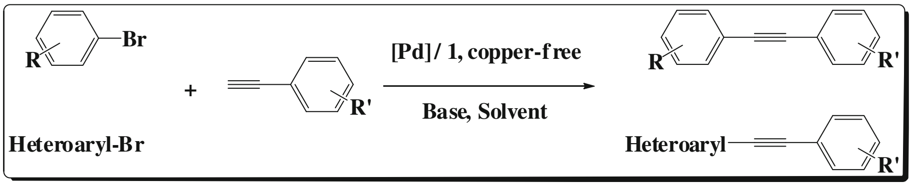


Fig. 2 Relationship between reaction conversion and ratio of 1 to [Pd]

Scheme 1 Copper-free Sonogashira reactions of phenyl/heteroaryl bromides with terminal alkynes



R = H, CF_3, CHO, $COCH_3$, CN, CH_3, OCH_3
R' = H, OCH_3, NO_2
Heteroaryl = pyridine, quinoline, pyrimidine

The change of **1**:[Pd] ratio was further investigated (Fig. 2). Being free of ligand, nearly no coupling product was detected; it is essential for the existence of ligand in the reaction. The highest conversion of 96 % (Table 1, entry 15) was obtained under the 1:1 ratio of **1** to [Pd]. As reported before, a possible η^4-Pd complex was formed under this ratio (1:1) and performed high activity in reaction [31]. Regardless of increasing or decreasing the ratio of **1** to [Pd], the concentration of η^4-Pd complex was reduced, leading to lower conversion.

On the basis of previous research, we subsequently moved our focus to expanding the scope of aryl bromides. Under the optimized condition, the reaction of both electron-withdrawing (Table 2, entries 1–10) and

Table 2 Scope of Sonogashira reactions of aryl bromides with terminal alkynes

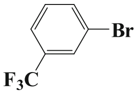
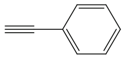
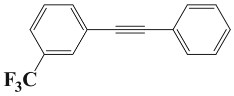
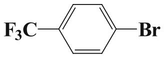
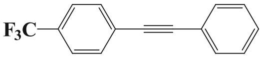
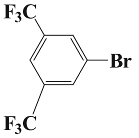
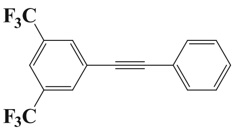
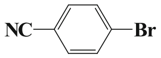
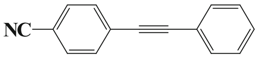
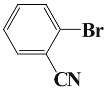
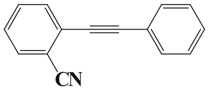
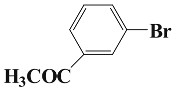
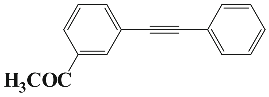
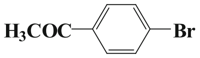
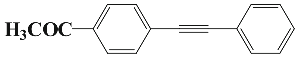
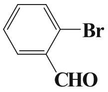
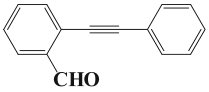
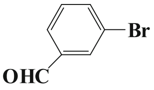
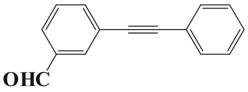
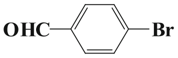
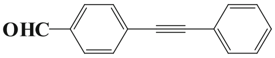
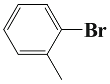
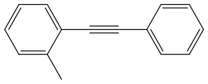
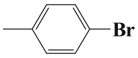
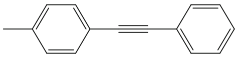
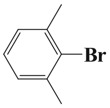
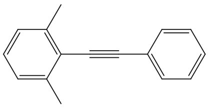
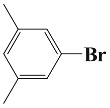
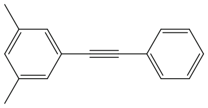
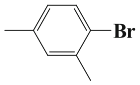
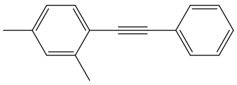
Entry	Aryl Bomide	Terminal Alkyne	Product	Yield (%)^a
1				91
2				94,(33)^b
3				92
4				99
5				89
6				98
7				98,(53)^b
8				94
9				97
10				96
11				88,(11)^b
12				89
13				90,(10)^b
14				93
15				89

Table 2 continued

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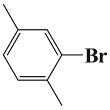
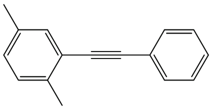
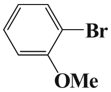
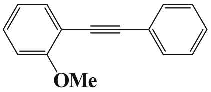
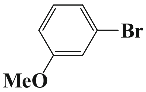
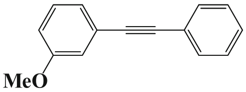
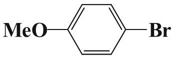
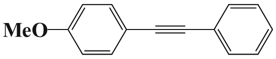
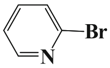
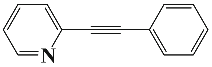
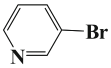
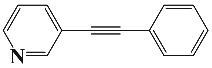
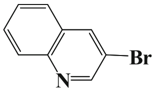
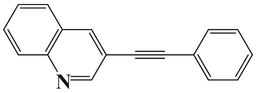
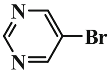
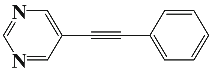
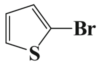
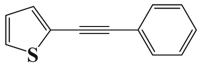
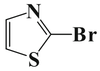
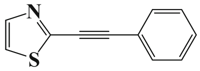
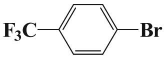
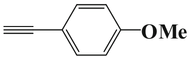
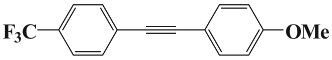
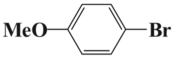
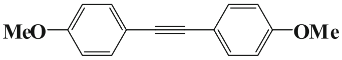
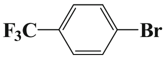
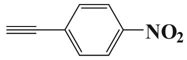
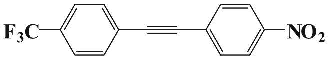
16				91
17				72
18				90
19				74
20				97,81[b],(31)[c]
21				95,61[b]
22				97
23				98
24				16
25				12
26				96
27				83
28				0

Reaction conditions: $[Pd(C_3H_5)Cl]_2$ (0.05 mol%), **1** (0.1 mol%), aryl bromide (1 mmol), terminal alkyne (1.2 *eq.*), K_3PO_4 (2 *eq.*), 1,4-dioxane (3 mL), 105 °C, 20 h

[a] Isolated yields based on aryl bromides. Data in parentheses are GC yields

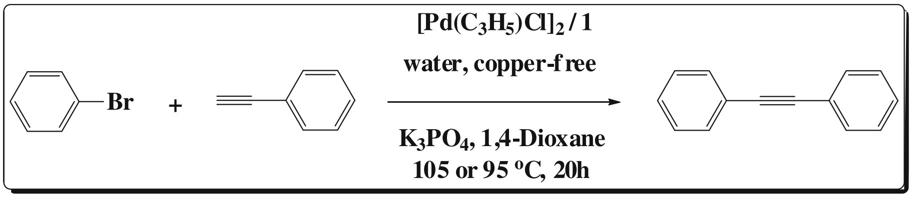
[b] 0.01 mol% of catalyst loading

[c] 0.001 mol% of catalyst loading

electron-donating (Table 2, entries 11–19) phenyl bromide derivatives gave desired products in good yields (up to 99 %). To the best of our knowledge, fewer study on the coupling of *o*-substituted phenyl bromides with phenylacetylene was reported, relatively contrary to the use of *m*- and *p*-substituted aryl bromides, and higher catalyst loading was usually required [27], whereas it is found that the reaction of *o*-substituted phenyl bromides with phenylacetylene still proceeded smoothly at a low palladium loading of 0.1 mol% in our system and satisfactory yields of 88–96% were obtained (Table 2, entries 5, 8, 11, 13 and 15–17). For instance reaction of 2-bromobenzonitrile afforded isolated yield of 89 % (Table 2, entry 5) while the literature reported was 22 % [27]. The relatively low yield of 72 % for 2-bromoanisole (Table 2, entry 17) might be ascribed to electron-donating effect rather than steric factor for 4-bromoanisole gave the similarly low yield of 74 % as well as 2-bromoanisole (Table 2, entry 19).

Compared to phenyl bromide derivatives, only a few couplings of heteroaryl bromides were reported. Copper-free protocols were even rarely studied, and they often required a high catalyst loading (up to 5 mol%) [19, 28, 29,

Scheme 2 Addition of water to the catalytic system



34–36]. We thereby tried to evaluate this catalyst on the copper-free coupling of heteroaryl bromides with phenylacetylene. Isolated yields of 95–98 % were obtained with bromopyridines (Table 2, entries 20, 21), 3-bromoquinoline (Table 2, entry 22) and 5-bromopyrimidine (Table 2, entry 23). When the catalyst loading was further decreased to 0.01 mol%, 2-bromopyridine still coupled efficiently with phenylacetylene to give yield of 81 %, and the yield of 31 % could be obtained with 0.001 mol% of catalyst (Table 2, entry 20). For 2-bromothiophen (Table 2, entry 24) and 2-bromothiazole (Table 2, entry 25), unfortunately, yields of only 16–12 % were obtained, respectively. The active species might be poisoned by the sulfur atom. In the end, the scope of terminal alkynes was also broadened. Induction of electron-donating group ($-OCH_3$) on phenylacetylene obviously accelerated the reaction, giving yield of 96 and 83 % with 4-bromobenzotrifluoride and 4-bromoanisole, respectively (Table 2, entries 26, 27). Contrarily, electron-withdrawing group ($-NO_2$) slowed down the reaction (Table 2, entry 28).

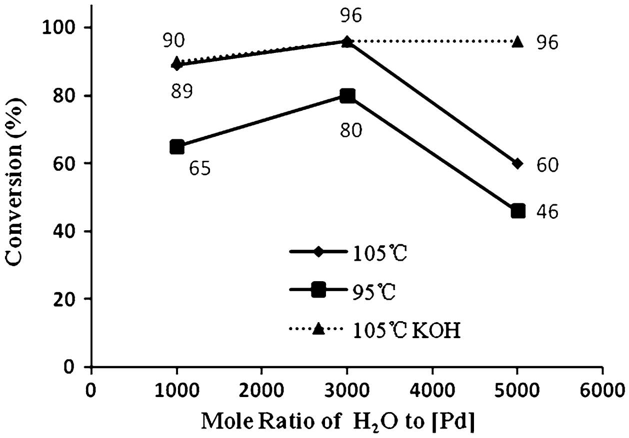
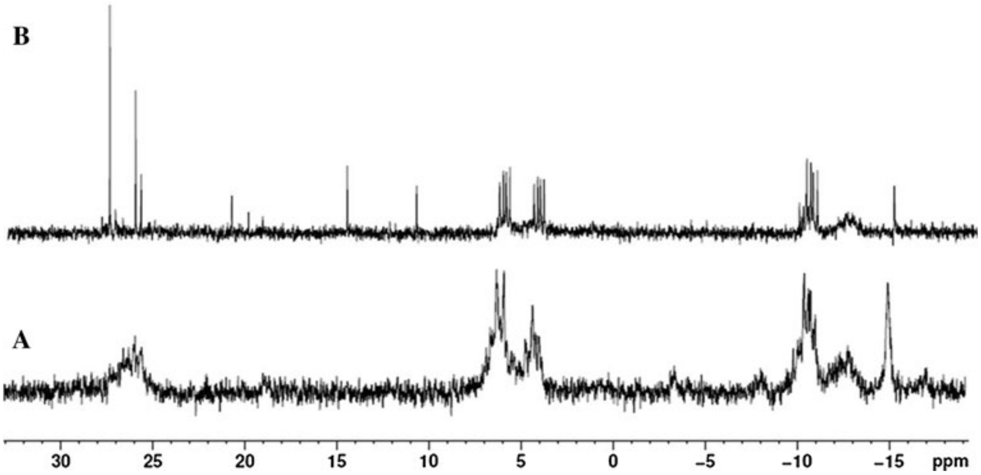


Fig. 3 Relationship between the conversion and mole ratio of H_2O to [Pd]

It was once reported that the addition of water could promote the coupling reaction [9]. Can water always benefit the reaction? We preliminarily investigated the influence of water on the reaction (Scheme 2) and concluded that appropriate water may promote the reaction while excess would hinder it (Fig. 3). In the absence of water, ^{31}P NMR experiment (Fig. 4) indicated that the species represented a fluxional behavior that displayed broad peaks on the spectrum. Therefore we assumed that P-Pd bond in η^4-Pd complexes bearing tetraphosphine was weak and the labile suffered a fast coordination-dissociation process [30, 31, 37, 38]. However, this process may be slowed down in the presence of excess water. As a result, splitted and sharp ^{31}P NMR peaks appeared at 26.1, 6.6, 4.4 and −15.1 ppm. Obviously, the addition of water changed the coordination microenvironment of Pd, and resulted in the structural transformation of the active species. Although it is not explicit that how water interacts with the Pd species, Santelli et al. had proved that the rapid structure transformation of Pd species bearing tetraphosphine was the key reason that Pd-Tedicyp system performed with highly

Fig. 4 ^{31}P NMR spectra of catalysts in situ



catalytic activity [30, 38]. In this case, the introduction of water in this system restrained the structural transformation of Pd species, but the appropriate amount of water promoted the catalytic activity. It was reasonable to suggest that the improvement of base solubility in solvent would led to the acceleration of the reaction. Finally the influence of water with the presence of a strong base KOH (Fig. 3) was investigated, and it was found that the promotional role of KOH was obviously stronger than K_3PO_4, especially in high ratio of water to Pd. The results proved that appropriate water improved the solubility of base and accelerated the reaction.

3 Conclusion

In summary, the tetraphosphine **1** in combination with $[Pd(C_3H_5)Cl]_2$ has been used in copper-free Sonogashira reactions. The highly efficient coupling reaction was carried out under optimized condition in the presence of a low catalyst loading and the excellent functional group tolerance was shown in this protocol. It was sightworthy that couplings of *o*-substituted phenyl and heteroaryl bromides performed smoothly in good yields. In addition, the coordination microenvironment of Pd might be changed by addition of water, and appropriate amount of water benefited, while excess water was unfavorable for the reaction.

4 Experimental

All catalytic reactions were carried out under the argon atmosphere. Solvents were purified by standard procedures and distilled prior to use. All starting materials were commercially available and were directly used without further purification. Catalyst precursors and **1** were prepared following reported methods. ^{31}P NMR and ^{1}H NMR spectra were recorded on Bruker AV II-400 MHz.

4.1 Preparation of Ligand 1 [39]

To a solution of $[Ph_2P(CH_2OH)_2]Cl$ (3.0 g, 10.6 mmol) in water (20 mL) was added excess triethylamine (3 mL) under N_2 atmosphere and ice bath condition, followed by addition of ethanol (40 mL) and ethane-1,2-diamine (178 µL, 2.6 mmol). The mixture was refluxed for 30 h. After the mixture cooled to room temperature, white precipitate was formed. The liquid was then filtered under N_2 and the precipitate was washed with water (2 × 10 mL) and cold ethanol (2 × 10 mL), and subsequently, recrystallized with CH_2Cl_2 and ethanol, yielding the product in 91 % (1.82 g, white solid). ^{31}P NMR (162 MHz, $CDCl_3$) δ: −28.4 (s). ^{1}H NMR (400 MHZ, $CDCl_3$) δ: 7.37–7.23 (m, 40H), 3.50 (d, 8H), 2.88 (s, 4H).

4.2 General Procedure for Sonogashira Reaction (Table 2, entry 2)

K_3PO_4 (424 mg, 2 mmol), 4-bromobenzotrifluoride (138 µL, 1 mmol) and phenylacetylene (130 µL, 1.2 *eq.*) were successively added into a dried Schlenk tube with a magnetic bar. Then DMF solution (0.1 mL) involved $[Pd(C_3H_5)Cl]_2$ (0.05 mol%)-**1** (0.1 mol%), and 1,4-dioxane (3 mL) was introduced through syringe. The mixture was heated to 105 °C and vigorously stirred for 20 h. At the end of the reaction, the mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layer was dried over $MgSO_4$(s), concentrated under vacuum and purified by silica gel column chromatography to yield the product in 94 %.

4.3 Investigation of the Ratio of 1 to [Pd] (Fig. 2)

Reagents: phenyl bromide (105 µL, 1 mmol), phenylacetylene (130 µL, 1.2 *eq.*), K_3PO_4 (424 mg, 2 *eq.*), DMF solution [0.1 mL, **1**-$[Pd(C_3H_5)Cl]_2$(0.05 mol%)] and 1,4-dioxane (3 mL). 105 °C, 20 h. Conversions are calculated according to GC based on the amount of phenyl bromide used.

4.4 Influence of Water Addition on the Reaction (Fig. 3)

Reagents: phenyl bromide (105 µL, 1 mmol), phenylacetylene (130 µL, 1.2 *eq.*), K_3PO_4 (424 mg, 2 *eq.*), DMF solution [0.1 mL, **1**(0.1 mol%)-$[Pd(C_3H_5)Cl]_2$(0.05 mol%)], 1,4-dioxane (3 mL) and water. 105 or 95 °C, 20 h. Conversions are calculated according to GC based on the amount of phenyl bromide used.

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