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PEG Click-Triazole Palladacycle: An Efficient Precatalyst for Palladium-Catalyzed Suzuki-Miyaura and Copper-free Sonogashira Reactions in Neat Water

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A novel water-soluble, phosphine-free PEG "click" triazole palladacycle has been successfully synthesized. As a precatalyst, the palladacycle exhibited superior catalytic activity towards Suzuki-Miyaura and copper-free Sonogashira cross-coupling in neat water with the turnover numbers (TONs) of up to 9.8×10^5. In addition, the catalyst could be reused at least 3 times without significant loss of reactivity.

Keywords palladium, cross-coupling, palladacycle, N-ligands, green chemistry

Introduction

Palladium-catalyzed cross-coupling reactions are one of the most robust and versatile methods for the formation of carbon-carbon and carbon-heteroatom bonds, which are crucial to build complex molecules such as natural products, agrochemicals, pharmaceuticals, and functional materials.[1] Over the past few decades, tremendous progress has been made in the development of catalysts for these transformations.[2] The well-developed highly electron-rich phosphine ligands provide excellent reactivity in the palladium-catalyzed cross-coupling reactions.[3] Despite their striking features, most of these phosphines compounds suffer from significant drawbacks such as air and/or moisture sensitivity, which limited their potential applications.[4] Meanwhile, in terms of green chemistry aspects,[5] using environmentally problematic phosphine ligands is ecologically unfavorable.

Since Herrmann and Beller reported the first palladacycle-catalyzed Heck and Suzuki-Miyaura reaction in 1995,[6] the palladacycle has emerged as a new class of versatile precatalysts for cross-coupling reactions. A wide variety of phosphine-free palladacycles with high catalytic activities have been developed which provided a promising alternative to phosphine ligands.[7] Working as a reservoir of palladium, palladacycle could release highly active Pd(0) species at a very slow rate, which prevents the deactivation of Pd(0) such as agglomeration, thus achieving high turn over numbers.[8]

As water is a readily available, nontoxic, and nonflammable solvent, the application of water as an environmentally benign reaction media has attracted numerous attention in recent years.[9] A series of water-soluble catalysts for reactions in aqueous media have been developed.[10] Among them, polyethylene glycol (PEG) modified catalysts/ligands, owning to their low toxicity, water solubility, and stability,[11] have found wide applications in cross coupling reactions.[12]

Currently, copper-catalyzed Huigen-type [3 + 2] azide–alkyne cycloaddition (CuAAC), the prototypical example of "click" reaction, owing to its high efficiency, simple work-up procedure, absence of side products and mild reaction conditions, has shown promising applications in drug discovery, biochemistry, material and polymer science.[13] Very recently, our studies on the dual-functional click-triazole ligand have revealed that the 1,2,3-triazole generated in the CuAAC reaction could serve as a stable linker as well as a chelator.[14]

Inspired by the notable features of palladacycle and PEG, we were intrigued to prepare a PEG-triazole-palladacycle, where the triazole motifs synthesized through the aforementioned "click" route might possibly acted as both a linker and a chelator. The resulting palladacycle might be endowed with remarkable catalytic reactivity as well as water solubility, thus could be used as a precatalyst for the palladium-catalyzed reaction in aqueous media.

Experimental

Catalyst preparation

Synthesis of PEG-OTs Monomethylated PEG_{5000} (10.000 g, 2.000 mmol) and toluene-4-sulfonyl chloride (TsCl) (3.813 g, 20.000 mmol) were dissolved in

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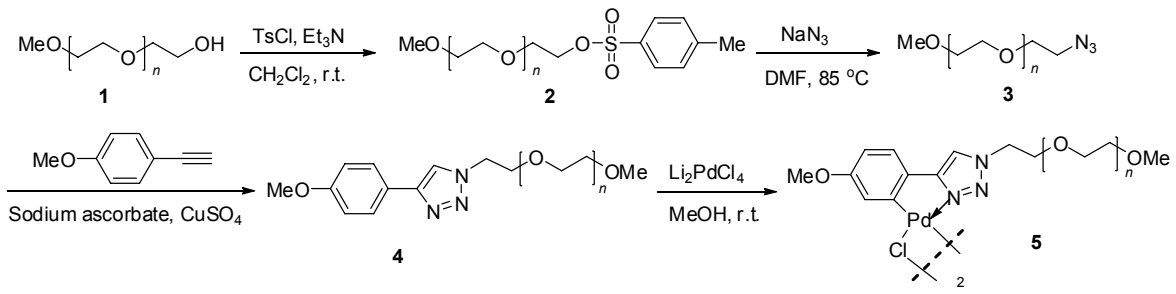
Scheme 1 Synthesis of PEG click triazole-palladacycle



CH_2Cl_2 (100 mL). Triethylamine (2.024 g, 20.000 mmol) was dissolved in CH_2Cl_2 (40 mL) and then slowly added to the above solution at ice-water bath. The mixture was allowed to stir at room temperature for 24 h and then precipitated into diethyl ether. After filtration under reduced pressure, then dried *in vacuo* at 35 ℃, the monotosylated poly(ethyleneglycol) (PEG-OTs) was obtained as white powder. Yield 9.412 g (91.2%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.77 (d, J=8.3 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 4.15−4.10 (m, 2H), 3.77−3.74 (m, 2H), 3.62 (s, 587H), 3.49−3.45 (m, 3H), 3.35 (d, J=2.2 Hz, 3H), 2.43 (s, 3H).

Synthesis of PEG-N_3 Sodium azide (2.080 g, 32.000 mmol) was added to a solution of PEG-OTs (8.230 g, 1.600 mmol) in DMF (50 mL) under a N_2 atmosphere. The reaction mixture was allowed to stir at room temperature for 24 h and then precipitated into diethyl ether. After filtration, the crude product was dissolved in CH_2Cl_2 and extracted sequentially with NaCl (5 wt%) solution and water, dried with anhydrous Na_2SO_4, and then precipitated in diethyl ether. After filtration under reduced pressure, the PEG-N_3 was obtained as white powder. Yield 7.160 g (87.7%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 3.79−3.73 (m, 2H), 3.62 (s, 338H), 3.49−3.45 (m, 2H), 3.35 (s, 3H).

Synthesis of PEG-triazole PEG-N_3 (5.025 g, 1.000 mmol) and 1-ethynyl-4-methoxybenzene (0.159 g, 1.200 mmol) were dissolved in DMF/water (15/15 mL) before sodium ascorbate (0.039 g, 0.200 mmol) and $CuSO_4$ (0.016 g, 0.100 mmol) were added. The resulting dispersion was stirred at room temperature for 24 h. Solvent was removed under reduced pressure, then the crude product was dissolved in CH_2Cl_2. After filtration the solution was extracted sequentially with NaCl (5 wt %) solution and water, dried with anhydrous Na_2SO_4, and then precipitated in diethyl ether. After filtration under reduced pressure, the PEG-triazole was obtained as white powder. Yield 4.740 g (90.7%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.81 (d, J=8.0 Hz, 2H), 6.96 (d, J=7.9 Hz, 2H), 4.60 (t, J=4.7 Hz, 2H), 3.92 (t, J=4.7 Hz, 2H), 3.84 (s, 3H), 3.79−3.75 (m, 2H), 3.63 (s, 521H), 3.51−3.46 (m, 2H).

Synthesis of PEG-triazole Palladacycle[15] PEG-triazole (2.610 g, 0.500 mmol) and NaOAc (0.041 g, 0.500 mmol) were added to the MeOH (10 mL) solution of Li_2PdCl_4 (0.132 g, 0.500 mmol), the resulting solution was stirred at room temperature for 24 h. Solvent was removed under reduced pressure, then the crude product was dissolved in CH_2Cl_2. After filtration the solution was extracted sequentially with NaCl (5 wt%) solution and water, dried with anhydrous Na_2SO_4, and then precipitated in diethyl ether. After filtration under reduced pressure, the dissolve-precipitation-filtration procedures were repeated 2 times before dried *in vacuo* at 35 ℃. The PEG-triazole palladacycle was obtained as white powder. Yield 2.370 g (86.0%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 8.33 (s, 2H), 7.95 (s, 2H), 7.02 (d, J=7.9 Hz, 4H), 4.64−4.59 (m, 4H), 3.89 (s, 11H), 3.63 (s, 1374H), 3.36 (s, 9H).

General procedure for Suzuki-Miyaura coupling reaction between aryl halides and arylboronic

Aryl halide (1.0 mmol), arylboronic acid (1.5 mmol) and K_2CO_3 (2.0 mmol) were added into a sealed tube, and 2.0 mL of water containing appropriate amount of catalyst was introduced. The solution was deoxygenated by purging with N_2 for 3 min. The reaction was stirred under reflux. After the reaction, the aqueous phase was extracted with ether for 4 times (2 mL×4). Then the combined organic layers were dried over anhydrous Na_2SO_4, concentrated under vacuum and purified by column chromatography to afford the desired product.

General procedure for Sonogashira coupling reaction between aryl halides and phenylacetylene

Aryl halide (1.0 mmol), phenylacetylene (1.5 mmol) and Cs_2CO_3 (2.0 mmol) were added into a sealed tube, and 2.0 mL of water containing appropriate amount of catalyst was introduced. The solution was deoxygenated by purging with N_2 for 3 min. The reaction was stirred at reflux. After the reaction, the aqueous phase was extracted with ether for 4 times (2 mL×4). Then the combined organic layers were dried over anhydrous Na_2SO_4, concentrated under vacuum and purified by column chromatography to afford the desired product.

Results and Discussion

The palladacycle was characterized by NMR spectroscopic analysis. As shown in Figure 1, all the aryl-proton signals shifted in a certain scale compared with the PEG-triazole, suggesting the coordination of PEG-triazole to the palladium. Moreover, the integral of

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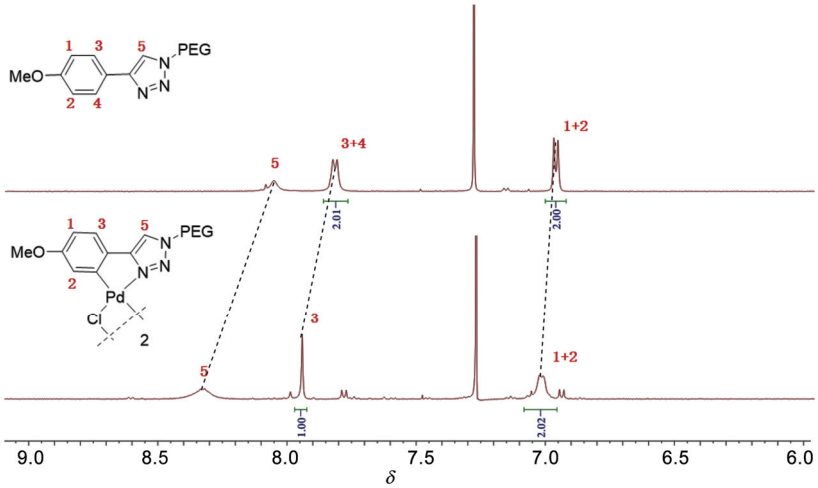


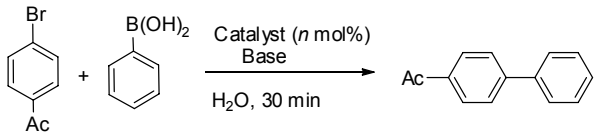
Figure 1 ^{1}H NMR of triazole and triazole-palladium complex.

aromatic protons decreased from 2H (triazole) to 1H (triazole palladium complex) which indicated the formation of Pd—C bond. The palladium amount of the palladacycle measured by inductively coupled plasma atomic emission spectrometry (ICP-MS) was 0.076 mmol/g.

With the palladacycle in hand, we turned our attention to evaluating its catalytic activity in aqueous Suzuki-Miyaura reaction. The screening of the reaction conditions was conducted with 1-(4-bromophenyl) ethan-1-one and phenylboronic acid as the model substrates, and the results are summarized in Table 1.

A 98% yield of biaryl product was obtained when the reaction was carried out with 0.05 mol% palladium loading in refluxed water for 30 min (entry 1). To our great surprise, an identical result was observed even with the palladacycle loading as low as 5×10^{-5} mol% (entry 2), representing a TON of 9.7×10^5. Meanwhile, employing Li_2PdCl_4 alone (entry 3) or Li_2PdCl_4 and PEG triazole at a 1∶1 ratio (entry 5) instead of palladacycle led to significant decreasing of cross-coupling yield. PEG triazole used alone (entry 4) has no catalytic activity at all. In addition, Hg drop test was also performed (entry 15). The Suzuki cross-coupling almost stopped in the presence of Hg^0, which indicated that colloidal Pd^0 generated from the palladacycle was the actual catalytic species.[16] A concurrent screen of bases (entries 6—11) revealed that the base has a crucial impact on cross-coupling reactions. Potassium salts such as K_2CO_3, KOH (entries 2, 8) displayed higher efficiency compared with the corresponding sodium salts (entries 6, 7). Carbonate salt, in addition to K_2CO_3 (entry 2), Cs_2CO_3 (entry 11) also gave a satisfying result. A slightly reduced reaction temperature did not significantly impair the yield (entry 12). However, reactions were greatly retarded at further reduced temperatures (entries 13, 14), presumably due to the poor dispersity of substrates in "cold" water. Herein, we obtained the optimal reaction conditions: aryl halide (1.0 mmol), arylboronic acid (1.5 mmol), palladacycle (0.00005 mol%), K_2CO_3 (2.0 mmol) and water (3.0 mL) under reflux.

Table 1 Optimization of reaction conditions[a]



Enter	Base	Catalyst	*n*	*T*/℃	Yield[b]/%
1	K_2CO_3	5	0.05	100	98
2	K_2CO_3	5	0.00005	100	98
3	K_2CO_3	Li_2PdCl_4	0.0001	100	19
4	K_2CO_3	4	0.0001	100	0
5	K_2CO_3	Li_2PdCl_4∶4 (1∶1)	0.0001	100	18
6	Na_2CO_3	5	0.00005	100	76
7	NaOH	5	0.00005	100	64
8	KOH	5	0.00005	100	92
9	NaOAc	5	0.00005	100	19
10	K_3PO_4	5	0.00005	100	26
11	Cs_2CO_3	5	0.00005	100	92
12	K_2CO_3	5	0.00005	80	95
13	K_2CO_3	5	0.00005	60	56
14	K_2CO_3	5	0.00005	40	5
15[c]	K_2CO_3	5	0.00005	100	＜5

[a] Reaction conditions: 1-(4-bromophenyl)ethan-1-one (1.0 mmol), phenylboronic acid (1.5 mmol), base (2.0 mmol), H_2O (3.0 mL). [b] Isolated yield based on aryl halide used. [c] 0.01g Hg was added.

Having obtained the optimized reaction conditions, we then embarked on an exploration of the substrate scope of the Suzuki-Miyaura reactions. A representative range of aryl halides and arylboronic acids were tested and the results are shown in Table 2. Generally, a wide range of coupling products were obtained with good to excellent isolated yields. For aryliodides with substituents such as —OMe, —NO_2, —F, —OH and —OMe (entries 1—6), nearly quantitative conversions were

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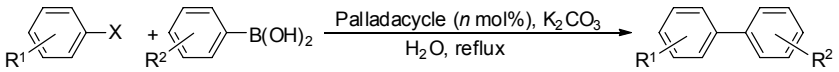
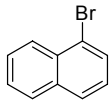
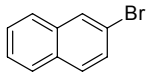
Table 2 Substrates scope of Suzuki-Miyaura cross-coupling[a]



Entry	R^1	X	R^2	*n*	Time/h	Yield[b]/%	TON
1	4-MeO	I	H	0.00005	0.5	93	9.3×10^5
2	3-NO_2	I	H	0.00005	0.5	98	9.8×10^5
3	4-NO_2	I	H	0.0005	0.5	95	9.5×10^4
4	4-F	I	H	0.00005	0.5	98	9.8×10^5
5	2-MeO	I	H	0.00005	0.5	98	9.8×10^5
6	4-$COCH_3$	I	H	0.00005	0.5	97	9.7×10^5
7	4-Me	I	H	0.0005	1	87	8.7×10^4
8	4-CH_2OH	Br	H	0.00005	0.5	98	9.8×10^5
9	4-Cl	Br	H	0.00005	0.5	90	9.0×10^5
10	4-H	Br	H	0.00005	0.5	97	9.7×10^5
11	4-Me	Br	H	0.0005	4	94	9.4×10^4
12	2-Me	Br	H	0.0005	4	98	9.8×10^4
13	3-Me	Br	H	0.0005	4	98	9.8×10^4
14	3-NO_2	Br	H	0.0005	4	79	7.9×10^4
15		Br	H	0.0005	4	83	8.3×10^4
16		Br	H	0.0005	4	78	7.8×10^4
17		Br	H	0.0005	4	81	8.1×10^4
18		Br	H	0.0005	4	91	9.1×10^4
19	4-NH_2	Br	H	0.005	8	90	9.0×10^3
20[c]	4-NO_2	Cl	H	0.05	12	77	7.7×10^2
21[c]	4-$COCH_3$	Cl	H	0.05	12	74	7.4×10^2
22	4-F	I	4-MeO	0.0005	4	96	9.6×10^4
23	4-F	I	4-OH	0.0005	4	96	9.6×10^4
24	4-$COCH_3$	Br	4-$COCH_3$	0.0005	8	98	9.8×10^4
25	4-CH_2OH	Br	4-$COCH_3$	0.0005	8	92	9.2×10^4
26	4-Cl	Br	4-$COCH_3$	0.0005	8	90	9.0×10^4
27	4-MeO	Br	4-$COCH_3$	0.0005	8	97	9.7×10^4
28	4-$COCH_3$	Br	4-CHO	0.0005	8	94	9.4×10^4
29	4-Me	Br	4-CHO	0.0005	8	83	8.3×10^4

[a] Reaction conditions: ArX (1.0 mmol), Ar-$B(OH)_2$ (1.5 mmol), K_2CO_3 (2.0 mmol), H_2O (3.0 mL). [b] Isolated yield based on aryl halide used. [c] 0.5 mmol TBAB was added.

observed and 93%—98% yields of the corresponding biaryl products were achieved within 30 min, with the TONs up to 9.8×10^5. However, a slightly lower yield was obtained when 1-iodo-4-methylbenzene was subjected to the system even with an elevated catalyst loading and prolonged reaction time (entry 7). Due to the different bond energy of C—Br and C—I, arylbromides are generally believed to be less reactive substrates in cross-coupling reactions compared with aryliodides.[17] To our delight, arylbromides such as benzene bromide, 1-bromo-4-chlorobenzene, (4-bromophenyl)methanol (entries 8—10) could afford results as

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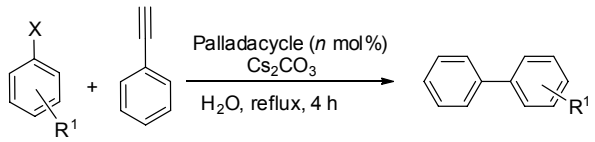
good as aryliodides do both in terms of yields and TONs. However, arylbromides with a methyl substituent required 0.0005 mol% catalyst loading to ensure satisfactory yields (entries 11—13). As demonstrated by entries 12, 17 and 15, 16, this catalytic system was also suitable for sterically hindered substrates and heteroaryl halides. Substituted aniline was proved to be a very reluctant coupling partner in Suzuki reaction,[18] 0.005 mol% palladacycle was required (entry 19). Additionally, we further investigated the coupling between arylchlorides and phenylboronic acid. 0.05 mol% catalyst loading and 0.5 equivalents of tetrabutylammonium bromide (TBAB) were needed for acceptable yields (entries 20, 21). The substrate scope of arylboronic acids was also explored (entries 22—29). To our satisfaction, all arylboronic acids and aryl halides tested underwent the coupling reactions efficiently, providing the desired products in good to excellent yields with the corresponding TONs of 9.0×10^4 to 9.8×10^4.

The successful application of palladacycle in Suzuki-Miyaura reaction encouraged us to move forward to extend this catalytic system for other palladium-catalyzed cross-coupling reactions, and a novel aqueous copper-free Sonogashira catalytic system was developed. With 0.05 to 0.1 mol% palladacycle as precatalyst, 2 equiv. Cs_2CO_3 as base, under refluxed reaction condition, various substituted aryliodides/bromides and ethynylbenzene were smoothly transformed into the corresponding diarylethynes (Table 3). Since no copper salt was added, the homocoupling of ethynylbenzene was avoided.

Table 3 Sonogashira cross-coupling of arylhalides and ethynylbenzene[a]

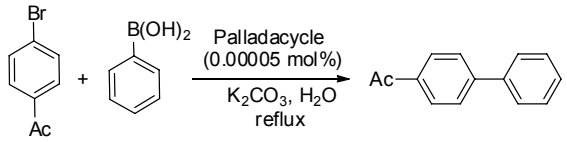


Entry	R^1	X	*n*	Yield[b]/%	TON
1	H	I	0.05	90	9.0×10^2
2	H	Br	0.05	91	9.1×10^2
3	4-Me	Br	0.1	87	4.4×10^2
4	4-Ph	Br	0.1	90	4.5×10^2
5	4-Cl	Br	0.1	83	4.2×10^2

[a] Reaction conditions: ArX (1.0 mmol), Phenylacetylene (2.0 mmol), Cs_2CO_3 (2.0 mmol), H_2O (3.0 mL). [b] Isolated yield based on aryl halide used.

Further experiments were conducted to investigate the recyclability of the catalyst. The use of water as solvent facilitated the separation of the product from reaction system. After the reaction of 4-bromobenzaldehyde and phenylboronic acid, the product and remaining substrates were extracted from aqueous phase with diethyl ether. The aqueous phase was charged with fresh substrates and base before the next run. As depicted in Table 4, the catalytic system could be reused at least 3 times before an unacceptable loss of reactivity was observed.

Table 4 Recyclability of the catalyst[a]



Cycle	Time/h	Yield[b]/%
1	0.5	98
2	1	94
3	2	90
4	4	75
5	6	60

[a] Reaction conditions: 1-(4-bromophenyl)ethan-1-one (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), K_2CO_3 (2.0 mmol), H_2O (3.0 mL), palladacycle (0.00005 mol%). [b] Isolated yield based on aryl halide used.

Conclusions

In conclusion, a novel PEG palladacycle was synthesized, which exhibited exceptionally high TONs in Suzuki-Miyaura cross-coupling of a broad scope of aryl halide and arylboronic acid in neat water. After removing the products by simple extraction, the catalyst could be reused for 3 times without significant loss of activity. Furthermore, the palladacycle was also capable for copper-free aqueous Sonogashira cross-coupling reactions with no homocoupling by-product being detected. This newly developed palladacycle precatalyst not only provided efficient protocols for palladium catalyzed cross-couplings in neat water, but also suggested a valuable approach for the design of palladacycle based on the dual-functional "click" triazole.

Acknowledgement

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