A robust hydrophilic pyridine-bridged bis-benzimidazolylidene palladium pincer complex: Synthesis and its catalytic application towards Suzuki–Miyaura couplings in aqueous solvents[†]

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A novel hydrophilic pyridine-bridged bis-benzimidazolylidene palladium pincer complex (3) acted as a highly efficient robust recyclable molecular catalyst towards Suzuki–Miyaura coupling reactions in aqueous media and tolerated various functional groups (even heterocycles) with extremely low catalyst loading.

N-heterocyclic carbenes (NHCs) and their metal complexes attracted increasing attention due to their wide application in catalysis, coordination chemistry and material sciences.^{1,2} Among them, pincer-type NHC palladium complexes constituted one of the prominent representatives owing to their robustness against air, moisture and heat.³ Although a large number of NHC palladium complexes have exhibited excellent catalytic activities in C-C bond formation reactions, their potential utility in aqueous solvents is neglected.⁴ Due to its unique properties such as inexpensive, environmentally-friendly and reusable, water is an attractive reaction media to replace other toxic organic solvents.⁵ Furthermore, it also allowed easy separation of the products and recirculation the water-soluble metallocyclic catalyst. Therefore, it is very important and challenging to develop suitable pincer-type NHC complexes and implement them as catalysts in the crosscoupling reactions under aqueous conditions.

Recently, we reported that pyridine-bridged palladium pincer complexes 1 (Scheme 1) and their precursors not only functionalized as efficient gelators for a variety of organic solvents and ionic liquids in extremely low gelator concentration and showed potential applications in gel catalysis and solar cells,^{6,7} but also demonstrated their powerful catalytic activities in homogenous C– C couplings even with catalyst loadings down to the ppm scale.^{8c} Although their steady carbon–metal bonds impose a high stability of these pincer complexes against water, they hardly gelate water



Scheme 1 Pyridine-bridged palladium pincer complexes.

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and catalyze the reactions in aqueous solvents due to a lack of hydrophilic groups. Polymer anchored pyridine-bridged imidazolylidene palladium complex 2a9 and its precursor analogues 2b10 (Scheme 1) have recently proved active and recyclable catalysts for Suzuki-Miyaura couplings only with electron-rich bromoarenes by Steel and Domínguez et al. Therefore, following our recent interest in developing novel pincer type NHC complexes and their potential application in catalysis and soft materials,⁶⁻⁸ we would like to introduce the carboxyl (COOH) as a hydrophilic group to tune the activity and solubility of the pincer palladacycles, which may further functionalize as organometallic hydrogelators and catalysts in aqueous media. Herein, we now report on a robust hydrophilic pyridine-bridged bis-benzimidazolylidene palladium complex 3 which is readily available from inexpensive starting materials and on its catalytic role towards Suzuki-Miyaura coupling reactions in aqueous solvents.



Scheme 2 Synthesis of palladium pincer complex 3.

The key precursor 4 could be easily accessed from commercially available citrazinic acid after bromination by PBr₃ and Br₂ with the assistance of P2O5.11 2,6-bis-Benzimidazolyl isonicotinic acid 5 was prepared through the cross-coupling reaction between benzimidazole and 4 catalyzed by CuI in dry DMF at 140 °C (concomitantly methyl ester was hydrolyzed into a carboxyl group),¹² and followed by installing alkyl chains to afford pyridinebridged bis-benzimdazolium dibromide 6. According to our previous procedure for NHC palladium complex 1, the pincertype palladacycle 3 is readily obtained in a moderate yield by microwave assisted palladation of the salt 6 with $Pd(OAc)_2$ in DMSO (Scheme 2).^{8c} Similar to complexes 1,^{6,13} the solubility of complex 3 in most organic solvents is not good, which may arise from the planarity of the complex favoring intermolecular stacking in the solid state, possibly enhanced by metal-metal bonding.⁶⁻⁸ However, with the help of the hydrophilic group, the solubility of complex 3 in alcohols and water is much better than complexes 1.

As part of our endeavour to manifest the applicability of novel metallocycles in catalysis and material sciences,⁶⁻⁸ we

Table 1	Suzuki-Miyaura	coupling	of 4-b	romoacetop	henon	with	aryl
boronic a	cids catalyzed by	palladium	pincer	complex 3 i	n watei	a	

	ArB(OH) ₂ + O_{F}	005 mol% 3 , CO ₃ , H ₂ O,100⁰C	- of O	Ar
			7aa-al	k
Entry	Ar	Time (h)	Product	Yield (%) ^b
1	Phenyl	3	7aa	>99
2	2-Tolyl	3	7ab	>99
3	3-Tolyl	3	7ac	>99
4	4-Tolyl	3	7ad	>99
5	2-Methoxyphenyl	3	7ae	94
6	3- Methoxyphenyl	3	7af	95
7	4- Methoxyphenyl	5	7ag	93
8	4-acetophonephenyl	5	7ah	>99
9	4-Flurorophenyl	3	7ai	>99
10	4-Trifluoromethylphenyl	3	7aj	>99
11	Naphthalen-2-yl	3	7al	98

firstly explored the catalytic role of complex 3 in the Suzuki-Miyaura couplings of para-bromoacetophenon with a variety of arylboronic acids in aqueous conditions. After optimization of the reaction conditions by choosing different bases and temperature, we found that with 50 ppm catalyst the coupling was accomplished within 3 h at 100 °C under aerobic conditions with K₂CO₃ or Cs₂CO₃ as a base (7aa: >99%, Table 1, entry 1). Inexpensive K_2CO_3 was then involved to investigate the substrate scope with various electronic and steric properties of arylboronic acids (Table 1, entries 2-11). The relative position of the mono-substituent hardly hindered the coupling process, ortho-, meta- and paratolyl (7ab-ad: >99%, Table 1, entries 2-4) and methoxyphenyl (7ae-ag: 93-95%, Table 1, entries 5-7) boronic acids resulted in similarly excellent yields. To our delight, the protocol also tolerated electron-deficient aryl boronic acids, quantitative yields were provided by para-acetophenonephenyl-, fluorophenyl and trifluoromethylphenyl boronic acids (7ah–aj: >99%, Table 1, entries 8–10). Furthermore, no significant steric implication was observed as shown for naphthalene-2-ylboronic acid which afforded a 98% yield (7al, Table 1, entry 11).

Inspired by these attractive results of various arylboronic acids, the influences of electronic and steric properties of electrophiles were next tested with a variety of (hetero)-bromoarenes. However, due to their low solubility in water, unsatisfied isolated yields were obtained with the insoluble electrophiles under optimal conditions (See ESI[†]). Although, only trace cross-coupling products were observed when MeOH was selected instead of H₂O under the standard conditions, additional MeOH in water did enhance the solubility of bromoarenes and increased the yields. After optimization, the best results were found in the coupling of phenyl boronic acid with bromobenzene when the ratio of H₂O-MeOH is 1:1 (7b: >99%, Table 2, entry 1). Therefore, the following reactions were carried out in the solvent mixture (H2O-MeOH) and revealed unapparent stereo-electronic effects (Table 2, entries 2-12). Ortho-, meta- and para-bromotoluene resulted in almost identical yields (7c-e: 97-98%, Table 2, entries 2-4). And methoxyl substrate also afforded an excellent isolated yield (7f: 99%, Table 2, entry 5). When *para*-bromochlorobenzene was applied, the coupling only occurred in the bromic terminal in a quantitative yield (7g, Table

Table 2Suzuki–Miyaura coupling of aryl bromides with phenyl boronicacid catalyzed by palladium pincer complex 3 in aqueous solvents^a

	ArBr + $B(OH)_2 = \frac{0.0}{K_2}$	05 mol% 3, CO ₃ , H ₂ O/MeOH 0°C,	Ar 7a-k	
Entry	Ar	Time/h	Product	Yield (%) ^b
1	Phenyl	3	7b	>99
2	2-Tolyl	3	7c	98
3	3- Tolyl	3	7d	98
4	4-Tolyl	3	7e	97
5	4- Methoxyphenyl	3	7f	99
6	4-Chlorophenyl	3	7g	>99
7	4- Cyanophenyl ^c	3	7h	99
8	4- (Ethoxycarbonyl)-phenyl ^e	3	7i	93
9	4- Fluorophenyl	3	7i	99
10	4- Nitrophenyl	12	7ĸ	>99
11	3,5-Bis(trifluoromethyl)-phen	yl 8	71	95
12	1-Bromonaphthalene	8	7m	95
13	Pyridin-3-yl	8	7n	83
14	Quinolin-3-yl	8	70	87

^{*a*} Reaction carried out in the mixture solvent ($H_2O-MeOH = 1:1$) under air. ^{*b*} Isolated yield. ^{*c*} Reaction carried out in water.

2, entry 6) which further demonstrated chloroarenes are not active with such low catalyst loading. As expected, very satisfactory results were obtained with all the electron-deficient mono- and di-substituted bromoarenes (**7h–1**, Table 2, entries 7–11), and hydro-sensitive substrates, such as *para*-bromobenzonitrile and ethyl 4-bromobenzoate, still endured aqueous reflux conditions and afforded excellent yields (**7h–i**: 93–99%, Table 2, entries 7 and 8). In addition, sterically more demanding substrates like 1-bromonaphthalene also resulted in 95% isolated (**7m**, Table 2, entry 12). With special interest for nicotine analogues which play an important role in pharmacy, chemistry and functional material science,¹⁴ *meta*-bromopyridine and bromoquinoline were also in this study and provided good yields demonstrating the high compatibility of the protocol even with heterocyclic substrates (**7n–0**: 83 and 87%, Table 2. entries 13–14)

A previous study on the Suzuki-Miyaura couplings catalyzed by palladium complexes 2b demonstrated that palladium nanoparticles acted as real catalytic species in the reaction.^{10a} However, the results of the heterocyclic bromoarenes with phenyl boronic acids (Table 2, entries 13-14) and our previous study on palladium pincer complexes^{8c} may suggest a molecular catalytically active species containing the pincer ligand was involved, similar to that previously reported by Crabtree.15 Consequently, a set of mercury tests was performed under optimal conditions with parabromoacetophenone and phenyl boronic acid in pure water. With 50 ppm catalyst loading, one drop of Hg (excess amount with respect to the palladium source) was added onto the reaction mixture after 0, 15, 30 and 45 min, it only retarded the reaction process and resulted in 61%, 84% 94% and 99% isolated yields respectively in 5-8 h (Table 3, entries 1-4) which indicated the transformation followed the pincer molecular catalytic route. Because of the efficient bonding ability of pyridine ligands to metallic palladium, the resulting insoluble complexes formed by ligands and metallic particles from the reaction mixture could absolutely inhibit the reaction process if nanoparticles were formed and acted as active species, an overdose of

Table 3	Poisoning	and	catalyst	minimizing	experiments	of	palladium
complex	3 catalyzed	Suzi	ıki–Miya	ura reaction	in water ^a		

	0 →−− Br + (B(OH) ₂ [Cat.] 3, K ₂ CO ₃ , H ₂ O, 100°C	} 7aa	\bigcirc		
Entry	Catalyst (mol%)	Additive or Note	Time (h)	Yield (%)		
1	0.005	Hg (1 drop after 0 min)	8	61		
2	0.005	Hg (1 drop after 15 min)	5	84		
3	0.005	Hg (1 drop after 30 min)	5	94		
4	0.005	Hg (1 drop after 45 min)	5	99		
5	0.005	PVPy (300 eq. of palladium)	5	92		
6	0.0008	TON: 1.188×10^5	24	95		
7	0.000008	TON: 7.625×10^{6}	96	61		
" All reaction were carried out in water under air ^b Isolated yield.						

poly(4-vinylpridine)(PVPy) was also included in the catalyst poisoning experiments.^{10a,16} Whereas, a 92% isolated yield further confirmed the molecular catalyst played the "real role" in the reaction, which is consistent with the results of the couplings with heterocyclic bromoarenes. The different active species derived from pyridine-bridged bis-benzimidazolylidene palladium complex **3** and its imidazolium analogues **2b** may arise from the stronger σ -donating property of benzimidazolylidene which stabilized the Pd–C and avoided the formation of Pd nanoparticles during the reflux.

As a practical protocol, the possibility of minimizing and recycling of the catalyst is the key issue. Decreasing the catalyst loading to 8 ppm, the model reaction resulted in a 98% isolated yield which extended the reaction time to 24 h (TON: 1.188×10^5 , Table 3, entry 6). Even with 8 ppb catalyst loading, the reaction still carried out very smoothly and a 61% isolated yield was observed for 7aa after 96 h (Table 3, entry 7). With these attractive results in hand, our attention was then focused on the recovery and reusability of the catalyst. Because of the insolubility of most products 7a-o in water, the solid biaryls were easily isolated by simply filtering after reaction and the filtrate containing catalyst 3 could be reused for the next catalytic cycle. By adding the substrates and base in the filtrate of the model reaction, there was no obvious loss of catalytic activity (up to three times) and almost quantitative yields were observed (See ESI[†]). Although, no palladium black appeared, the yield of the further run dropped dramatically which may be caused by catalyst loss during filtration.

In conclusion, a robust hydrophilic pyridine-bridged bisbenzimidazolylidene pincer palladium complex **3**, which is readily accessible from inexpensive and commercial precursors, demonstrated excellent catalytic activity towards Suzuki–Miyaura coupling reactions and tolerated a variety of functional groups varying in their electronic and steric properties in aqueous media with a catalyst loading down to the ppm scale. As a practical and environmentally-friendly protocol, the products could be easily separated after reaction by simple filtration and the filtrate could be reused as a catalyst several times. In contrast to imdazolium analogues, the palladium pincer complex **3** acts as a molecular catalyst, which may be attributed to the steady Pd–C imposed by the stronger σ -donating property of benzimidazolylidene compared to imidazolylidene and hardly broken to form Pd nanoparticles during the reaction process.

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