



REGULAR ARTICLE

Highly efficient aqueous-phase Sonogashira coupling catalyzed by Pd-PEPPSI/PPh₃ under aerobic condition

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Abstract. An *in situ* generated catalytic system comprised of a Pd-PEPPSI [Pyridine enhanced pre-catalyst preparation, initiation, and stabilization] complex, (NHC)PdBr₂(Pyridine), and PPh₃ co-ligand demonstrated excellent activity for the Sonogashira cross-coupling reactions between phenylacetylene with aryl halides in neat water under the aerobic condition in presence of CuI as co-catalyst. The catalytic system was not only compatible with electronically diverse aryl bromides/ iodides but also effective for relatively difficult substrates like heteroaryl bromides. Notably, under similar experimental conditions, the mixed PEPPSI/PPh₃ system displayed superior activity over the free Pd-PEPPSI or Pd-phosphine system.

Keywords. Cross-coupling; carbene ligands; palladium; PEPPSI; sonogashira reaction.

1. Introduction

The palladium-catalyzed Sonogashira coupling reactions of aryl halides with terminal alkynes have surfaced as a transformative strategy for the preparation of substituted and conjugated alkynes.^{1,2} Normally, the reaction proceeds in the presence of CuI as a co-catalyst and had been widely employed to prepare building blocks that find applications in agrochemicals, pharmaceuticals, and material science.³ In recent years, several modifications of the original Sonogashira protocol have been devised to expand the scope of these reactions. The most concentrated efforts have been made to eliminate the copper co-catalyst as it forms reactive copper acetylide which renders it difficult to operate the reaction under aerobic conditions.^{4,5} On the other hand, attempts have also been made to perform the reaction exclusively using copper as it is advantageous from an economic point of view due to its low cost.⁶ Despite considerable efforts, palladium metal with copper salts/complexes is still employed for this coupling reaction as this catalytic system is highly compatible with a wide range of functional groups under mild conditions.⁷ However,

the major drawback of many of these conventional approaches is the formation of homocoupling product of acetylene as a side product.^{9,10} Literature evidence suggests that the problem of homocoupling could be circumvented by selecting an appropriate ligand system with Pd. Among them, N-heterocyclic carbenes⁵ and phosphine^{4,8} based ligands are noteworthy.

Over the past few years, well-defined monoligated palladium (II) NHC complexes with ancillary nitrogen ligands have gained considerable interest due to their stability against moisture and air and have been explored for different cross-couplings such as Suzuki-Miyaura,⁹ Mizoroki-Heck,¹⁰ and Sonogashira reactions.⁵ To improve the catalytic performance of NHC-based complexes, the synergic ligand effects between NHCs and additive ligands have also been investigated.¹¹ Recent research in the groups of Jamison,¹² Cazin,¹³ and others¹⁴ highlights the co-operative ligand effects between phosphine and NHCs in nickel and palladium mediated cross-coupling reactions and affirmed that π -acceptor phosphine based ligands could modulate the electronic properties of NHCs which facilitates faster reductive elimination and improve the reactivity and selectivity of the catalyst.

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Following this exciting concept, during the past few years, a huge array of mixed phosphine palladium NHC complexes has been developed and explored their utility in Sonogashira cross-couplings.¹⁵ However; most of these protocols employ organic solvents as a reaction medium. From economic and environmental standpoints, these organic solvents are not considered as ideal reaction media due to their high cost, toxicity, non-biodegradability, and inflammable nature. To address these environmental and safety concerns, in the last few years, catalytic systems based on palladium NHCs have been developed to perform C–C bond-forming reactions in water.¹⁶ As water is highly abundant, cheap, and non-toxic, in the past few decades, a great impetus has been given to perform organic reactions in water.¹⁶ Moreover, conducting organic reactions in water can often demonstrate a hydrophobic effect that leads to an enhancement in reaction rate.¹⁸ In sharp contrast to earlier belief, several palladium-catalyzed reactions have been successfully employed in water, and in some cases, the rate accelerating effects have also been observed.¹⁹ However, there exist only a few examples of Pd-NHC based catalytic systems, both homogeneous and heterogeneous, for Sonogashira cross-couplings in an aqueous medium,^{5h,5i,15a,17a,17b} although majority of those systems required the addition of an organic co-solvent with water to maximize product yield.^{5h,5i,15a,17a,17b} To the best of our knowledge, there is only one palladium-NHC based catalytic system reported for the Sonogashira cross-coupling reaction in neat water.^{17a} The major advantage of the system was that the coupling reaction could be performed without the addition of copper co-catalyst with a relatively low catalyst loading (0.5 mol%). However, the principal limitation of the system was its narrow substrate scope as it was applicable only for simple aryl iodides; difficult substrates like heteroaryl iodide or aryl bromides had not been investigated. Thus, the development of robust and easy to prepare palladium NHC catalysts for the aqueous phase Sonogashira reaction without the addition of an organic co-solvent is of tremendous significance.

Herein, we report the efficiency of Pd-PEPPSI, **1** in the Sonogashira reaction in presence of triphenylphosphine (1 mol%) and CuI (10 mol%) with a low loading of catalyst (1 mol%) in an aqueous medium under aerobic condition. Recently, we have reported that **1** is highly efficient for Mizoroki-Heck reaction in an aqueous medium and the yield of the products was obtained up to 95%.²⁰ Considering the impressive performance of catalyst **1** in Mizoroki-Heck reaction, we were encouraged to explore its

catalytic efficiency in the Sonogashira reaction (Scheme 1).

2. Experimental

2.1 Materials and methods

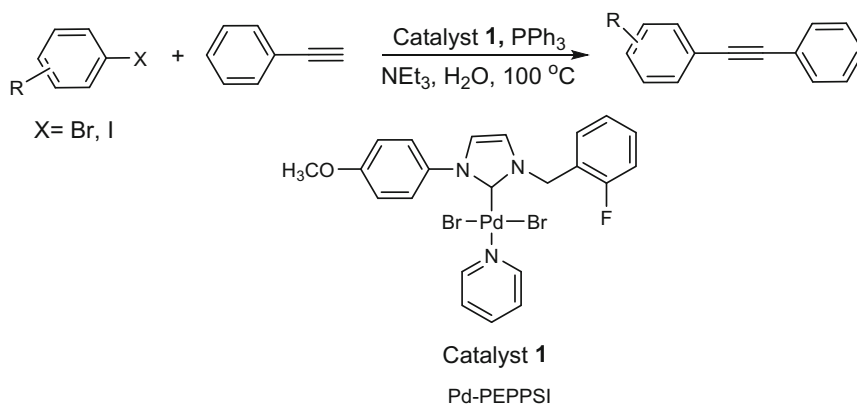
Unless specified, all substrates were commercially available and directly used without further purification. The ligand and the complex were synthesized by following our reported procedure.²⁰ (4-methoxyphenyl)-1H-imidazole and 2-fluorobenzyl bromide were purchased from Sigma-Aldrich. PdCl₂ used for the preparation of the complex was purchased from TCI. Solvents, substrates for catalysis and bases were purchased from various commercial firms like TCI, Sigma-Aldrich and Merck. The conversion of the product was determined by GC-MS (Agilent 7820A GC, 5975 MSD mass detector) analysis. All catalytic reactions were carried out under aerobic conditions.

2.2 Procedure for preparation of 3-(2-fluorobenzyl)-1-(4-methoxyphenyl)-1H-imidazolium bromide (L)

A round bottom flask (50mL) was charged with (4-methoxyphenyl)-1H-imidazole (174 mg, 1 mmol), 2-fluorobenzyl bromide (1.89 g, 10 mmol) and 5 mL CH₃CN. The reaction mixture was heated at 80 °C for 48 h and then allowed to cool to room temperature. Diethyl ether was added to obtain a precipitate. The precipitate was recovered by filtration and the solid was washed with diethyl ether thrice. Yield: 268 mg (74%) white powder

2.3 Procedure for the preparation of PEPPSI-Pd-NHC (Catalyst 1) complex

A round bottom flask (50 mL) was charged with imidazolium salt L (218 mg, 0.6 mmol), PdCl₂ (89 mg, 0.5 mmol), K₂CO₃ (207 mg, 1.5 mmol), excess KBr, and pyridine (5 mL). The mixture was heated under stirring conditions for 48 h. The reaction mixture was allowed to cool to room temperature and then the solvent was removed under vacuum. The solid mass was dissolved in dichloromethane (DCM) and filtered. The complex was purified through column chromatography, eluting with DCM/hexane (7:3). Complex 1: Yield 265 mg, (70%); yellow powder



Scheme 1. Palladium aqueous Sonogashira reaction under aerobic condition.

2.4 General procedure of the Sonogashira reaction

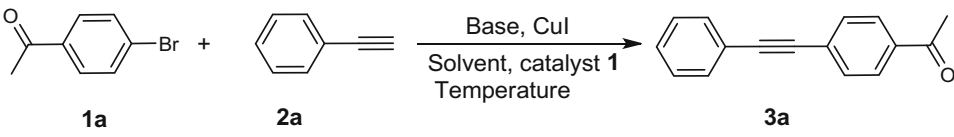
A 50 mL reaction flask was charged with 1 mmol of an aryl bromide/iodide, 1.2 mmol of phenylacetylene, 1 mmol of a base, 4 mL of water, and 1 mol% of catalyst **1**. The mixture was stirred at 100 °C for the required time. The reaction was monitored with TLC and finally, organic products were extracted with ethyl acetate (3 × 15 mL) from the reaction mixture through biphasic extraction and dried over Na₂SO₄. The identities of the products and their conversions were confirmed by GC-MS (Agilent 7820A GC, 5975 MSD mass detector) analysis.

3. Results and Discussion

To investigate the efficacy of catalyst **1** and to identify the optimized conditions for the proposed cross-coupling reactions, we had selected 4-bromoacetophenone (**1a**) and phenylacetylene (**2a**) as model substrates. The initial cross-coupling reaction was carried out in DMF at 80 °C with 1 mol% of catalyst **1** in presence of CuI (10 mol%) and triethylamine (TEA) as a base under aerobic conditions (Table 1, entry 1). After the completion of 24 h of reaction time, a 39% conversion of desired product was observed. However, when the reaction was performed at a slightly elevated temperature (100 °C), the conversion of the desired cross-coupling product increased marginally (Table 1, entry 3). It needs to be mentioned that CuI played a significant role in this catalytic process as the conversion of the product was decreased when the reaction was carried out in absence of it (Table 1, entry 2). As we know, in transition metal-based catalytic reactions; solvents play a paramount role and determine the

overall performance of the catalytic reactions. Therefore, to identify the best solvent for our catalytic process, we had carried out the model reaction with a range of solvents and the corresponding results are noted in Table 1. Generally, low conversions were observed when the reaction was carried out in organic solvents such as DMF, acetonitrile, toluene, and DMSO (Table 1, entries 3-6). However, 56% conversion of the desired cross-coupling product was obtained in refluxing THF (Table 1, entry 7). Pleasingly, when the reaction was carried out in refluxing water, the conversion of the product increased to 64% (Table 1, entry 8). As, there is literature precedent suggesting that the introduction of additional ligand triphenylphosphine with palladium NHC complexes bearing throw-away ligand increases the efficiency of the reaction in the Sonogashira cross-coupling reaction, therefore, we were intrigued to explore the role of this additional phosphine ligand in our catalytic system.^{15e} To our delight, when the reaction of **1a** with **2a** was performed in water at 100 °C under the same set of conditions, in presence of 1 mol% of triphenylphosphine, the conversion of the product increased to 78% (Table 1, entry 9). However, a further increase in the amount of triphenylphosphine did not have any effect on the reaction outcome (Table 1, entry 10). The study on the effect of reaction temperature and catalyst loading reveals that with a decrease in reaction temperature or catalyst loading, the conversion of the cross-coupling product decreases (Table 1, entries 14, 17). Likewise, when the influence of nature of the bases on the reaction outcome was evaluated, we were surprised to notice that choice of the base has a significant influence on our catalytic reaction.

Among the bases used [triethylamine (TEA), Cs₂CO₃, K₂CO₃, and NaOH], triethylamine was found to

Table 1. Optimization of reaction parameters for Pd-PEPPSI catalyzed Sonogashira reaction^a.


Entry	Base	Solvent	Temperature (°C)	PPh ₃ (mol%)	Conversion ^b (%)	Time (h)
1	Et ₃ N	DMF	80	–	39	24
2 ^c	Et ₃ N	DMF	80	–	17	24
3	Et ₃ N	DMF	100	–	45	24
4	Et ₃ N	Toluene	100	–	32	24
5	Et ₃ N	CH ₃ CN	Reflux	–	42	24
6	Et ₃ N	DMSO	120	–	48	24
7	Et ₃ N	THF	Reflux	–	56	24
8	Et ₃ N	H ₂ O	100	–	64	24
9	Et ₃ N	H ₂ O	100	1	78	24
10	Et ₃ N	H ₂ O	100	2	77	24
11	NaOH	H ₂ O	100	1	38	24
12	K ₂ CO ₃	H ₂ O	100	1	Trace	24
13	Cs ₂ CO ₃	H ₂ O	100	1	Trace	24
14 ^d	Et ₃ N	H ₂ O	100	1	54	24
15	Et ₃ N	H ₂ O	100	1	78	12
16	Et ₃ N	H ₂ O	100	1	42	6
17	Et ₃ N	H ₂ O	80	1	52	12
18 ^e	Et ₃ N	H ₂ O	100	1	00	12
19 ^f	Et ₃ N	H ₂ O	100	–	Trace	12

^aReaction condition: Phenylacetylene (1.2 mmol), 4-bromoacetophenone (1 mmol), Base (1mmol), CuI (10 mol%), Solvent (4 mL).

^bConversion is determined by GC-MS (measured as the conversion of 4-bromoacetophenone to products).

^cabsence of CuI.

^d0.5 mol% of **1**.

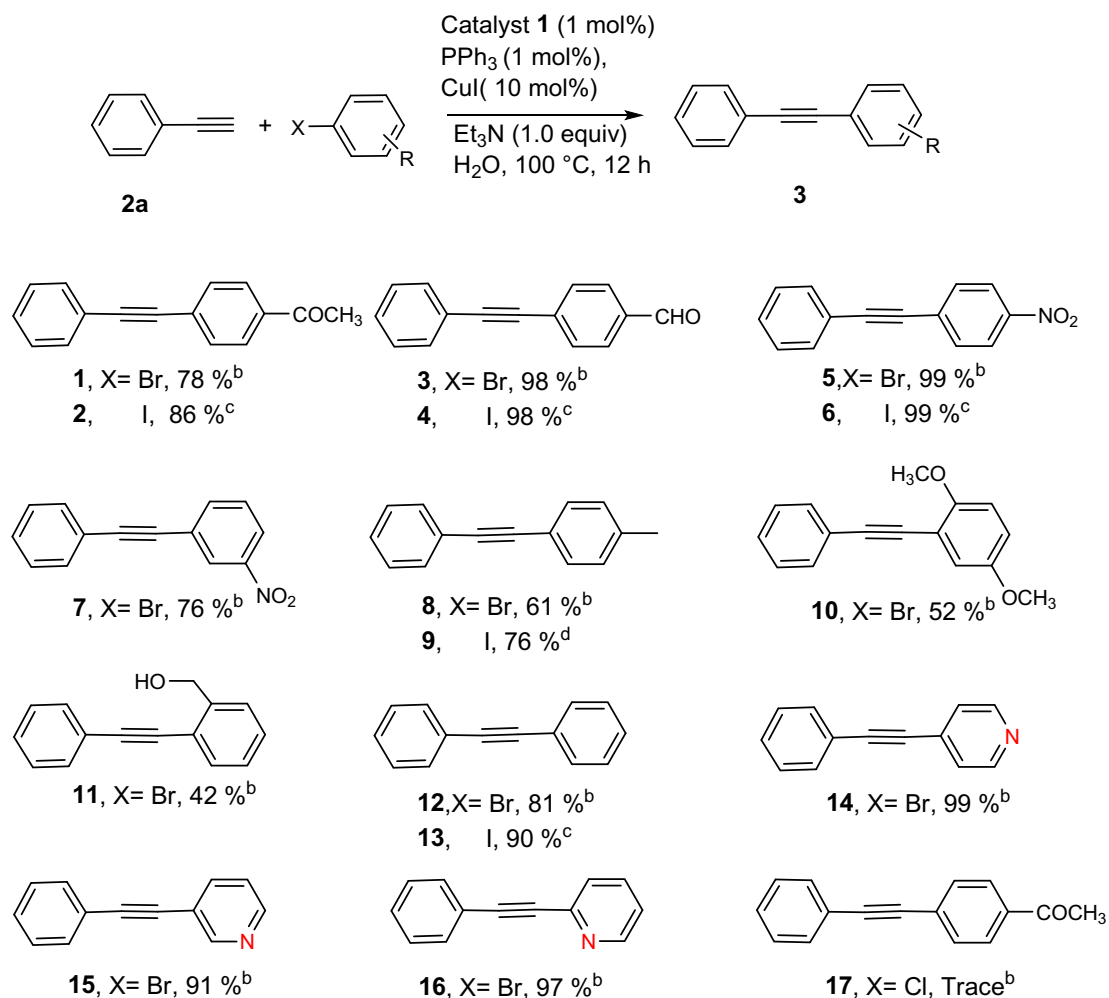
^eabsence of **1**.

^f1 mol% of PdBr₂(PPh₃)₂.

be most effective while Cs₂CO₃ and K₂CO₃ were virtually inactive and did not render the cross-coupling product (Table 1, entries 9, 11–13). Although the reaction was initially performed for 24 h, the time-dependent conversion study disclosed that maximum conversion of the product was achieved within 12 h and further extension of reaction time, did not improve the reaction outcome (Table 1, entry 15). It is noteworthy to mention that in absence of catalyst **1**, no product was observed (Table 1, entry 18). After the extensive screening of reaction parameters such as solvent, temperature, base and catalyst loading, and reaction time, the optimum conditions for our catalytic process were found to be 1 mol% of catalyst **1**, 10 mol% of CuI, PPh₃ (1 mol%) in the water at 100 °C, with 1.5 equivalents of Et₃N for 12 h (Table 1, entry 15). Finally, when we performed the benchmark reaction under our optimized conditions with 1 mol%

of Pd (PPh₃)₂Br₂, only a trace amount of desired cross-coupling product was detected (Table 1, entry 19). This result substantiates the activity of catalyst **1** in the Sonogashira cross-coupling reaction.

After establishing the optimum reaction conditions, to evaluate the scope and limitations of our catalytic process, we have performed several representative cross-coupling reactions of aryl bromides/iodides with phenylacetylene, and the results are summarized in Scheme 2. As shown in Scheme 2, the aryl bromides/iodides with electron-donating, neutral, and electron-withdrawing groups are efficiently coupled with phenylacetylene, furnishing the substituted alkynes in good to excellent conversions. In general, the reactions with aryl iodides delivered the cross-coupling products in a short reaction time compared to aryl bromides (Scheme 2, 1, 3, 5, 8, 12 Vs 2, 4, 6, 9, 13). Aryl bromides or iodides bearing electron-withdrawing



Scheme 2. Sonogashira cross-coupling of phenylacetylene with aryl bromides/iodides (Reaction condition: Phenylacetylene (1.2 mmol), aryl bromides/iodides (1 mmol), Et₃N (1mmol), CuI (10 mol%), water (4 mL), Conversion % is determined by GC-MS (measured as the conversion of aryl halides to products).

groups at para position (Scheme 2, 1-6) smoothly reacted with phenylacetylene and gave excellent conversions of expected products, while aryl bromides/iodides containing electron-donating group such as methyl gave comparatively lower yield (**8**, **9**). Similarly, the aryl bromide bearing -NO₂ group at meta position gave a lower yield compared to its para analog (**7** Vs **5**). Under our optimized conditions, the sterically hindered substrates such as 2,5-dimethoxybromobenzene and 2-bromobenzyl alcohol were compatible and gave moderate yields (**10**, **11**). Finally, we had extended our catalytic protocol to heteroaryl bromides. It needs to be mentioned that heteroaryl bromides are considered as difficult substrates in Sonogashira cross-coupling reactions and often give low yield. However, high conversions of the desired products were observed, when 4-bromopyridine, 3-bromopyridine, and 2-bromopyridine were allowed to react with phenylacetylene under our

optimal conditions (**14-16**). Unfortunately, our catalytic method failed to deliver the cross-coupling product when chloroarene was employed as the coupling partner in water (**17**).

4. Conclusions

In summary, we have developed a green and user-friendly catalytic method for the Sonogashira coupling of aryl bromides/iodides and phenylacetylene in neat water under aerobic conditions by using low loading of Pd-PEPPSI complex in presence of CuI, triphenylphosphine, and triethylamine base. Interestingly, this catalytic method is compatible with various sterically and electronically different aryl bromides/iodides including heteroaryl bromides to furnish substituted alkynes under aerobic conditions in neat water.

Supplementary Information (SI)

The SI includes GC-MS of the Sonogashira products. Figures S1–S19 are available at www.ias.ac.in/chemsci.

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References

- Chinchilla R and Najera C 2011 Recent advances in Sonogashira reactions *Chem. Soc. Rev.* **40** 5084
- Doucet H and Hierso J C 2007 Palladium-based catalytic systems for the synthesis of conjugated enynes by sonogashira reactions and related alkynylations *Angew Chem. Int. Ed.* **46** 834
- (a) Chinchilla R and Najera C 2007 The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry *Chem. Soc. Rev.* **107** 874; (b) Negishi E and Anastasia L 2003 Palladium-Catalyzed Alkynylation *Chem. Rev.* **103** 1979; (c) Sonogashira K 2002 Development of Pd-Cu catalyzed cross-coupling of terminal acetylenes with sp^2 -carbon halides *J. Organomet. Chem.* **653** 46; (d) Liu J, Lam J W Y and Tang B Z 2009 Acetylenic Polymers: Syntheses, Structures, and Functions *Chem. Rev.* **109** 5799; (e) Kim T and Swager T M 2003 A Fluorescent Self-Amplifying Wavelength-Responsive Sensory Polymer for Fluoride Ions *Angew. Chem., Int. Ed.* **42** 4803
- Selected examples (a) Torborg C, Huang J, Schulz T, Schaffner B, Zapf A, Spannenberg A, Borner A and Beller M 2009 Improved Palladium-Catalyzed Sonogashira Coupling Reactions of Aryl Chlorides *Chem. Eur. J.* **15** 1329; (b) Böhm V P W and Herrmann W A 2000 A Copper-Free Procedure for the Palladium-Catalyzed Sonogashira Reaction of Aryl Bromides with Terminal Alkynes at Room Temperature *Eur. J. Org. Chem.* 3679; (c) Pu X, Li H and Colacot T J 2013 Heck Alkynylation (Copper-Free Sonogashira Coupling) of Aryl and Heteroaryl Chlorides, Using Pd Complexes of $t\text{-Bu}_2(p\text{-NMe}_2\text{C}_6\text{H}_4)\text{P}$: Understanding the Structure-Activity Relationships and Copper Effects *J. Org. Chem.* **78** 568; (d) Yi C and Hua R 2006 Modified Palladium-Catalyzed Sonogashira Cross-Coupling Reactions under Copper-, Amine-, and Solvent-Free Conditions *J. Org. Chem.* **71** 2535; (e) Lipshutz B H, Chung D W and Rich B 2008 Sonogashira Couplings of Aryl Bromides: Room Temperature, Water Only, No Copper *Org. Lett.* **10** 3793; (f) Soheili A, Albaneze-Walker J, Murry J A, Dormer P G and Hughes D L 2003 Efficient and General Protocol for the Copper-Free Sonogashira Coupling of Aryl Bromides at Room Temperature *Org. Lett.* **5** 4191; (g) Ma Y, Song C, Jiang W, Wu Q, Wang Y, Liu X and Andrus M B 2003 Sonogashira Coupling Using Bulky Palladium-Phenanthryl Imidazolium Carbene Catalysis *Org. Lett.* **5** 3317
- (a) Yang L, Guan P, He P, Chen Q, Cao C, Peng Y, Shi Z, Pang G and Shi Y 2012 Synthesis and characterization of novel chiral NHC-palladium complexes and their application in copper-free Sonogashira reactions *Dalton Trans.* **41** 5020; (b) Samantaray M K, Shaikh M M and Ghosh P 2009 Copper-free and amine-free Sonogashira coupling in air in a mixed aqueous medium by palladium complexes of N/O -functionalized N-heterocyclic carbenes *J. Organomet. Chem.* **694** 3477; (c) John A, Modak S, Madasu M, Katari M and Ghosh P 2013 Palladium complexes of the N-fused heterocycle derived abnormal N-heterocyclic carbenes for the much-preferred Cu-free and the amine-free Sonogashira coupling in air *Polyhedron* **64** 20; (d) Yang L, Li Y, Chen Q, Du Y, Cao C, Shi Y and Pang G 2013 Sonogashira/hydroarylation sequential reactions: catalyzed by NHC-Pd complexes *Tetrahedron* **69** 5178; (e) Martek A, Gazvoda M, Urankar D and Kosmrlj J 2020 Designing Homogeneous Copper-Free Sonogashira Reaction through a Prism of Pd-Pd Transmetalation *Org. Lett.* **22** 4938; (f) İmik F, Yaşar S and Özdemir I 2019 Synthesis of bridged palladium-PEPSSI complexes and catalytic studies in C-C cross-coupling reactions *Inorg. Chim. Acta* **495** 118969; (g) Lu H, Wang L, Yang F, Wua R and Shen W 2014 Cross-coupling reactions catalyzed by an N-heterocyclic carbene-Pd (II) complex under aerobic and CuI-free conditions *RSC Adv.* **4** 30447; (h) John A, Shaikh M M and Ghosh P 2009 Palladium complexes of abnormal N-heterocyclic carbenes as precatalysts for the much preferred Cu-free and amine-free Sonogashira coupling in air in a mixed-aqueous medium *Dalton Trans.* 10581; (i) Dash C, Shaikh M M and Ghosh P 2009 Fluoride-Free Hiyama and Copper- and Amine-Free Sonogashira Coupling in Air in a Mixed Aqueous Medium by a Series of PEPSSI-Themed Precatalysts *Eur. J. Inorg. Chem.* **12** 1608
- Selected examples (a) Zou L H, Johansson A J, Zuidema E and Bolm C 2013 Mechanistic Insights into Copper-Catalyzed Sonogashira-Hagihara-Type Cross-Coupling Reactions: Sub-Mol % Catalyst Loadings and Ligand Effects *Chem. Eur. J.* **19** 8144; (b) Li T, Qu X, Xie G and Mao J 2011 $[\text{Cu}(\text{acac})_2]\cdot\text{H}_2\text{O}$ -Catalyzed Sonogashira-Type Couplings of Aryl Halides and Terminal Alkynes *Chem. Asian J.* **6** 1325; (c) Lin C H, Wang Y J and Lee C F 2010 Efficient Copper-Catalyzed Cross-Coupling Reaction of Alkynes with Aryl Iodides *Eur. J. Org. Chem.* 4368; (d) Zuidema E and Bolm C 2010 Sub-Mol % Catalyst Loading and Ligand-Acceleration in the Copper-Catalyzed Coupling of Aryl Iodides and Terminal Alkynes *Chem. Eur. J.* **16** 4181; (e) Biffis A, Tubaro C, Scattolin E, Basato M, Papini G, Santini C, Alvarez E and Conejero S 2009 Trinuclear copper (I) complexes with triscarbene ligands: catalysis of C-N and C-C coupling reactions *Dalton Trans.* 7223; (f) Monnier F, Turtaut F, Duroure L and Taillefer M 2008 Copper-Catalyzed Sonogashira-Type Reactions Under Mild Palladium-Free Conditions *Org. Lett.* **10** 3203; (g) Liu Y, Blanchard V, Danoun G,

- Zhang Z, Tlili A, Zhang W, Monnier F, Lee A V D, Mao J and Tailleurfer M 2017 Copper-Catalyzed Sonogashira Reaction in Water *ChemistrySelect* **2** 11599; (h) Cao Y, Dong X-Y, Yang J, Jiang S. P, Zhou S, Li Z L, Chen G O and Liu X Y 2020 A Copper-Catalyzed Sonogashira Coupling Reaction of Diverse Activated Alkyl Halides with Terminal Alkynes Under Ambient Conditions *Adv. Synth. Catal.* **362** 2280
7. (a) Z Gonda, G L Tolnai and Z Novák 2010 Dramatic Impact of ppb Levels of Palladium on the “Copper-Catalyzed” Sonogashira Coupling *Chem. Eur. J.* **16** 11822; (b) Gallop C W D, Chen M-T and Navarro O 2014 Sonogashira Couplings Catalyzed by Collaborative (N-Heterocyclic Carbene)-Copper and -Palladium Complexes *Org. Lett.* **16** 3724; (c) Shen A, Wu Z, Fang Y, Yang J, Zhu H and Tu T 2018 A Concerted Catalytic System for Sonogashira Coupling Reactions: Combination of N-Heterocyclic Carbene Palladium and Copper Complexes *Asian J. Org. Chem.* **7** 1113
 8. (a) Handa S, Smith J D, Zhang Y, Takale B S, Gallou F and Lipshutz B H 2018 Sustainable HandaPhos-ppm Palladium Technology for Copper-Free Sonogashira Couplings in Water under Mild Conditions *Org. Lett.* **20** 542; (b) Jin B, Gallou F, Reilly J and Lipshutz B H 2019 ppm Pd-catalyzed, Cu-free Sonogashira couplings in water using commercially available catalyst precursors *Chem. Sci.* **10** 3481
 9. Selected examples (a) Aktaş A, Celepci D B, Gök Y and Aygün M 2018 2-Hydroxyethyl-Substituted Pd-PEPPSI Complexes: Synthesis, Characterization and the Catalytic Activity in the Suzuki–Miyaura Reaction for Aryl Chlorides in Aqueous Media *ChemistrySelect.* **3** 9974; (b) Lu D-D, He X-X and Liu F S 2017 Bulky Yet Flexible Pd-PEPPSI-IPent^{An} for the Synthesis of Sterically Hindered Biaryls in Air *J. Org. Chem.* **82** 10898; (c) Ouyang J S, Li Y F, Huang F D, Lu D-D and Liu F S 2017 The Highly Efficient Suzuki–Miyaura Cross-Coupling of (Hetero)aryl Chlorides and (Hetero)arylboronic Acids Catalyzed by “Bulky-yet-Flexible” Palladium-PEPPSI Complexes in Air *ChemCatChem.* **10** 371; (d) Erdemir F, Celepci D B, Aktaş A and Gök Y 2019 2-hydroxyethyl-substituted (NHC)PdI₂(pyridine) (Pd-PEPPSI) Complexes: Synthesis, Characterization and the Catalytic Activity in the Sonogashira Cross-coupling Reaction *ChemistrySelect* **4** 5585; (e) Benhamou L, Besnard C, Kündig E P 2014 Chiral PEPPSI Complexes: Synthesis, Characterization, and Application in Asymmetric Suzuki–Miyaura Coupling Reactions *Organometallics* **33** 260; (f) Rajabi F, Trampert J, Sun Y, Busch M, Bräse S and Thiel W R J 2013 Synthesis and characterization of a 4-nitrophenyl functionalized NHC ligand and its palladium (II) complex *J. Organomet. Chem.* **744** 101; (g) Rajabi F and Thiel W R 2014 An Efficient Palladium N-Heterocyclic Carbene Catalyst Allowing the Suzuki–Miyaura Cross-Coupling of Aryl Chlorides and Arylboronic Acids at Room Temperature in Aqueous Solution *Adv. Synth. Catal.* **356** 1873; (h) Li D-H, He X-X, Dong F-D, Liu N, Shen D-S and Liu F-S 2019 N-Heterocyclic Carbene Palladium Complexes with Dianisole Backbones: Synthesis, Structure, and Catalysis *Organometallics* **38** 2539; (i) Tu T, Sun Z, Fang W, Xu M and Zhou Y 2012 Robust Acenaphthoimidazolylidene Palladium Complexes: Highly Efficient Catalysts for Suzuki–Miyaura Couplings with Sterically Hindered Substrates *Org. Lett.* **14** 4250; (j) Chen M T, Vicic D A, Turner M L and Navarro O 2011 (N-Heterocyclic Carbene)PdCl₂(TEA) Complexes: Studies on the Effect of the “Throw-Away” Ligand in Catalytic Activity *Organometallics* **30** 5052; (k) Chen M-T and Kao Z-L 2017 Effect on orthometallation of NHC palladium complexes toward the catalytic activity studies in Suzuki coupling reaction *Dalton Trans.* **46** 16394
 10. Selected examples (a) Lin Y-C, Hsueh H-H, Kanne S, Chang L-K, Liu F-C, Lin I J B, Lee G-H and Peng S-M 2013 Efficient PEPPSI-Themed Palladium N-Heterocyclic Carbene Precatalysts for the Mizoroki–Heck Reaction *Organometallics* **32** 3859; (b) Gao T-T, Jin A-P and Shao L-X 2012 N-Heterocyclic carbene-palladium (II)-1-methylimidazolylidene complex catalyzed Mizoroki–Heck reaction of aryl chlorides with styrenes *Belistein. J. Org. Chem.* **8** 1916; (c) Lu H, Wang L, Yang F, Wua R and Shen W 2014 Cross-coupling reactions catalyzed by an N-heterocyclic carbene–Pd (II) complex under aerobic and CuI-free conditions *RSC Adv.* **4** 30447; (d) Keske E C, Zenkina O V, Wang R and Crudden C M 2012 Synthesis and Structure of Palladium 1,2,3-Triazol-5-ylidene Mesoionic Carbene PEPPSI Complexes and Their Catalytic Applications in the Mizoroki–Heck Reaction *Organometallics* **31** 6215
 11. (a) Vougioukalakis G C and Grubbs R 2010 Ruthenium-Based Heterocyclic Carbene-Coordinated Olefin Metathesis Catalysts *Chem. Rev.* **110** 1746; (b) Gaillard S and Renaud J-L 2013 When phosphorus and NHC (N-heterocyclic carbene) meet each other *Dalton Trans.* **42** 7255
 12. Ho C Y and Jamison T F 2007 Highly Selective Coupling of Alkenes and Aldehydes Catalyzed by [Ni(NHC){P(OPh)₃}]: Synergy between a Strong σ Donor and a Strong π Acceptor *Angew. Chem., Int. Ed.* **46** 782
 13. Diebolt O, Jurcík V, da Costa R C, Braunstein P, Cavallo L, Nolan S P, et al. 2010 Mixed phosphite/N-heterocyclic carbene complexes: synthesis, characterization and catalytic studies *Organometallics* **29** 1443
 14. (a) Toselli N, Martin D and Buono G 2008 Looking for a Synergic Effect between NHCs and Chiral P-Ligands *Org. Lett.* **10** 1453; (b) Zhang J, Xu J, Xu Y, Sun H, Shen Q and Zhang Y 2015 Mixed NHC/Phosphine Ni (II) Complexes: Synthesis and Their Applications as Versatile Catalysts for Selective Cross-Couplings of ArMgX with Aryl Chlorides, Fluorides, and Methyl Ethers *Organometallics* **34** 5792; (c) Kim M, Shin T, Lee A and Kim H 2018 Synergistic Ligand Effect between N-Heterocyclic Carbene (NHC) and Bicyclic Phosphoramidite (Briphos) Ligands in Pd-Catalyzed Amination *Organometallics* **37** 3253
 15. (a) Aktas A, Erdemir F, Celepci D B, Gok Y and Aygun M 2019 Mixed phosphine/N-heterocyclic carbene-palladium complexes: synthesis, characterization, crystal structure and application in the Sonogashira reaction in aqueous media *Transit. Metal. Chem.* **44** 229; (b) Bourbakri L, Yasar S, Dorcet V, Roisenel T, Bruneau C, Hamadi N and Ozdemir I 2017 Synthesis and catalytic

- applications of palladium N-heterocyclic carbene complexes as efficient pre-catalysts for Suzuki-Miyaura and Sonogashira coupling reactions *New. J. Chem.* **41** 5105; (c) Touj N, Yasar S, Ozdemir N, Hamdi N and Ozdemir I 2018 Sonogashira cross-coupling reaction catalysed by mixed NHC-Pd-PPh₃ complexes under copper free conditions *J. Organomet. Chem.* **860** 59; (d) Boubakri L, Mansour L, Harrath A H, Ozdemir I, Yasar S and Hamdi N 2018 N-Heterocyclic carbene-Pd(II)-PPh₃ - complexes as a new highly efficient catalyst system for the Sonogashira cross-coupling reaction: Synthesis, characterization and biological activities *J. Coord. Chem.* **71** 183; (e) Batey R A, Shen M and Lough A J 2002 Carbamoyl-Substituted N-Heterocyclic Carbene Complexes of Palladium (II): Application to Sonogashira Cross-Coupling Reactions *Org. Lett.* **4** 1411
16. (a) Levin E, Ivry E, Disendruck C E and Lemcoff N G 2015 Water in N-Heterocyclic Carbene-Assisted Catalysis *Chem. Rev.* **115** 4602; (b) Wang W, Cui L, Sun P, Shi L, Yue C and Li F 2018 Reusable N-Heterocyclic Carbene Complex Catalysts and Beyond: A Perspective on Recycling Strategies *Chem. Rev.* **118** 9843
 17. (a) Zhang C, Liu J and Xia C 2015 Easily prepared water soluble Pd-NHC complex as an efficient, phosphine-free palladium catalyst for the Sonogashira reaction *Chin. J. Catal.* **36** 1387; (b) Roy S and Plenio H 2010 Sulfonated N-Heterocyclic Carbenes for Pd-Catalyzed Sonogashira and Suzuki-Miyaura Coupling in Aqueous Solvents *Adv. Synth. Catal.* **352** 1014; (c) Gazvoda M, Virant M, Pevac A, Urankar D, Bolje A, Kocevar M and Kosmrlj J 2016 A mesoionic bis(Py-tzNHC) palladium (II) complex catalyses "green" Sonogashira reaction through an unprecedented mechanism *Chem. Commun.* **52** 1571
 18. (a) Bhattacharya S and Sengupta S 2004 Palladium catalyzed alkynylation of aryl halides (Sonogashira reaction) in water *Tetrahedron Lett.* **45** 8733; (b) Breslow R 1991 Hydrophobic effects on simple organic reactions in water *Acc. Chem. Rev.* **24** 159
 19. Selected examples (a) Turner G L, Moris J A and Greaney M F 2007 Direct Arylation of Thiazoles on Water *Angew. Chem., Int. Ed.* **119** 8142; (b) Krasovskaaya V, Krasovskiy A, Bhattacharjya A and Lipshutz B H 2011 "On water" sp³-sp² cross-couplings between benzylic and alkenyl halides *Chem. Commun.* **47** 5717; (c) Ohnmacht S A, Mamone P, Culshaw A J and Greaney M F 2008 Direct arylations on water: synthesis of 2, 5-disubstituted oxazoles balsoxin and texaline *Chem. Commun.* 1241; (d) Simon M-O and Li C-J 2012 Green chemistry oriented organic synthesis in water *Chem. Soc. Rev.* **41** 1415
 20. Borah D, Saha B, Sarma B and Das P 2020 A new PEPPSI type N-heterocyclic carbene palladium (II) complex and its efficiency as a catalyst for Mizoroki-Heck cross-coupling reactions in water *J. Chem. Sci.* **132** 51