



Palladium(II) phthalocyanines efficiently promote phosphine-free Sonogashira cross-coupling reaction at room temperature

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ABSTRACT

Herein we report that exceptionally simple and inexpensive Pd(II) complexes of phthalocyanines efficiently catalyze direct formation of diphenylacetylenes at ambient conditions with low loading of catalyst (0.5 mol%). Results of this study demonstrate that terminal alkynes reacted mildly with *p*-substituted aryl bromides at room temperature under Pd and Cu-cocatalysis to give the corresponding phenylacetylenes in yields up to 98%. Also we have examined this catalyst in Sonogashira cross-coupling with aryl chlorides and it was very effective and this reaction at room temperature that there is no examples in recent articles. This protocol represents the first use of palladium phthalocyanine as homogeneous catalyst in the Pd/Cu-promoted Sonogashira reaction. The palladium(II) phthalocyanine complex is significantly more active in Sonogashira cross-coupling between aryl halides and terminal alkynes as compared with traditional catalysts because of absence of palladium black formation through agglomeration of metal particles and deactivation of catalyst.

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1. Introduction

Alkynes are among the most versatile functional groups [1,2] and are widely present in natural compounds [3,4], drugs [5], and organic materials [6]. Therefore, the development of methods for the introduction of alkyne groups onto organic molecules is of high importance. To this end, the Sonogashira coupling reaction is the most general method for the formation of multiple bonds from aryl or alkenyl (pseudo)halides and terminal alkynes [7–11]. This approach has become the most important reaction to the construction of different scaffolds containing triple bonds, which are essential moieties in the creation of various natural products, heterocyclic compounds, pharmaceuticals, and materials [12–15]. Creation of aromatic compounds with π -expanded system gives the possibility of the employment of these molecules in different organic photovoltaic devices, as nonlinear optical materials [16–21], in sensing [21], and in molecular electronics [22,23]. Synthesis of various diphenylacetylenes by Sonogashira Pd-catalyzed cross-coupling of terminal acetylenes with aryl halides is key method for solution of this problem. To present time, a big number of combinations of different factors and parameters have been made in the original protocol [24–31], in which Heck and Sonogashira pub-

lished a Pd- or Pd/Cu-catalyzed coupling of a terminal alkyne or alkene with an aryl halides [26–33]. At recent time, the synthetic potential of the Sonogashira reaction is significantly expanded and diversity of substrates can be used in this method. It should be noted that in spite of big variety of palladium catalysts there is serious problem which is associated with precipitation of inactive Pd metal particles (Pd black) during the reaction. High initial catalyst amounts, hard conditions, low reaction rates will initiate the agglomeration of palladium particles and very low catalytic activity [34,35].

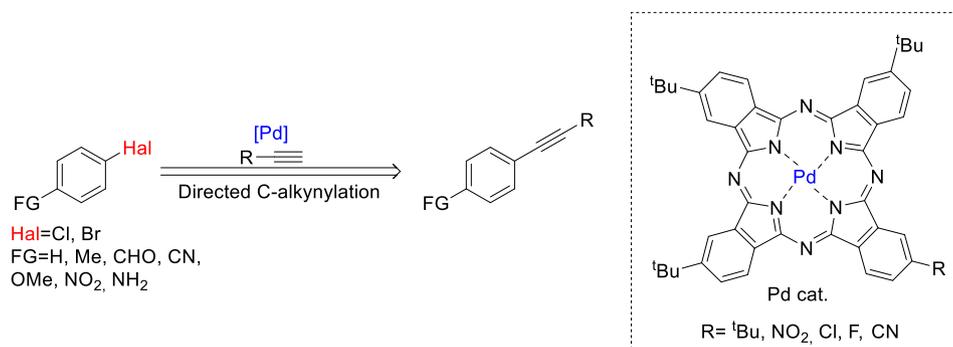
Here we report synthesis various diphenylacetylenes via direct alkynylation with use Sonogashira cross-coupling reaction and new generation palladium catalysts based on macrocyclic phthalocyanine ligand (Scheme 1). We also demonstrate for the first time that amino group in 4-bromoaniline doesn't participate in palladium-catalyzed C–N coupling with formation of bis(4-bromophenyl)amine that is associated with mild conditions of reaction and low loading of catalyst.

2. Results and discussion

In this article we synthesized new palladium complexes of *tert*-butyl-substituted phthalocyanines and used as catalysts in palladium-catalyzed reaction of terminal acetylenes with aryl halides. We have prepared tetra-*tert*-butyl-substituted and

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Scheme 1. C-alkynylation with terminal acetylenes under palladium catalysis and Sonogashira coupling conditions.

unsymmetrical A₃B-type phthalocyanines containing electron withdrawing groups (F, Cl, NO₂, CN) for determination of their influence on catalytic activity of complexes. The choice of these complexes as ligands is associated with high solubility in various organic solvents and stability in solutions in wide range of temperatures. It should also be noted that an additional reason for obtaining palladium(II) A₃B-type phthalocyanines was very poor solubility of tetra-substituted analogs in most organic solvents even at heating.

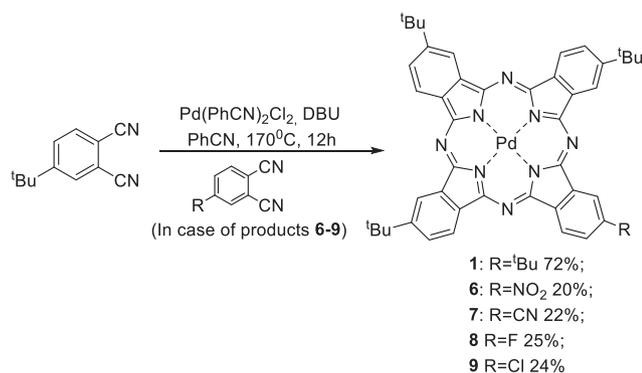
These complexes are good catalytic model systems for use in cross-coupling reaction, because they don't catalyze process in precatalytic condition and «homeopathic release» of high active palladium species to prevent formation of palladium black during the reaction. It also should be noted that palladium complexes with macrocyclic ligands such as phthalocyanines and porphyrines possess good solubility and chemical stability in wide range of temperatures that is very favor for use in different catalytic processes.

The palladium complex of tetra-*tert*-butyl-substituted phthalocyanine **1** was prepared via one-step protocol based on metal-catalyzed template synthesis from easy available

4-*tert*-butyl phthalonitrile (Scheme 2). The synthesis of complex **1** was carried out by using of excess of bis(benzonitrile)palladium(II) dichloride and DBU as base at heating in anhydrous benzonitrile during 12 h. The control of reaction was monitored by TLC (silica, dichloromethane) and UV–Vis spectroscopy. After completion of the reaction, reaction mixture was cooled, solvent was evaporated *in vacuo* and target complex **1** was isolated by column chromatography on silica.

In case of unsymmetrical A₃B-type phthalocyanines containing mono electron withdrawing group, target palladium complexes were prepared by mixed condensation

4-*tert*-butylphthalonitrile with 4-nitrophthalonitrile, 4-cyanophthalonitrile,



Scheme 2. Synthetic pathway for preparation of palladium(II) phthalocyanines.

4-fluorophthalonitrile or 4-chlorophthalonitrile respectively in conditions of template synthesis (Scheme 3) with 20–25% yields. It should be noted that low yields of palladium complexes of A₃B-type phthalocyanines is associated with limitation of this method because of statistically formation of products mixture (A₄, A₃B, A₂B₂). 4-Nitrophthalonitrile was synthesized by nitration reaction of phthalimide with fuming nitric acid in sulfuric acid and following two-step formation of nitrile group (Scheme 3) [36]. 4-Chloro- and 4-cyanophthalonitrile were obtained via diazotiation of 4-aminophthalonitrile with good yields by known literature methods (Scheme 3) [37]. We used Balz-Schiemann reaction for synthesis of 4-fluorophthalonitrile, which is based on formation of diazonium tetrafluoroborate salt through diazotiation reaction of 4-aminophthalonitrile with nitrosonium tetrafluoroborate with following its decomposition at heating in 1,2-dichlorobenzene with 70% yield (Scheme 3) [38].

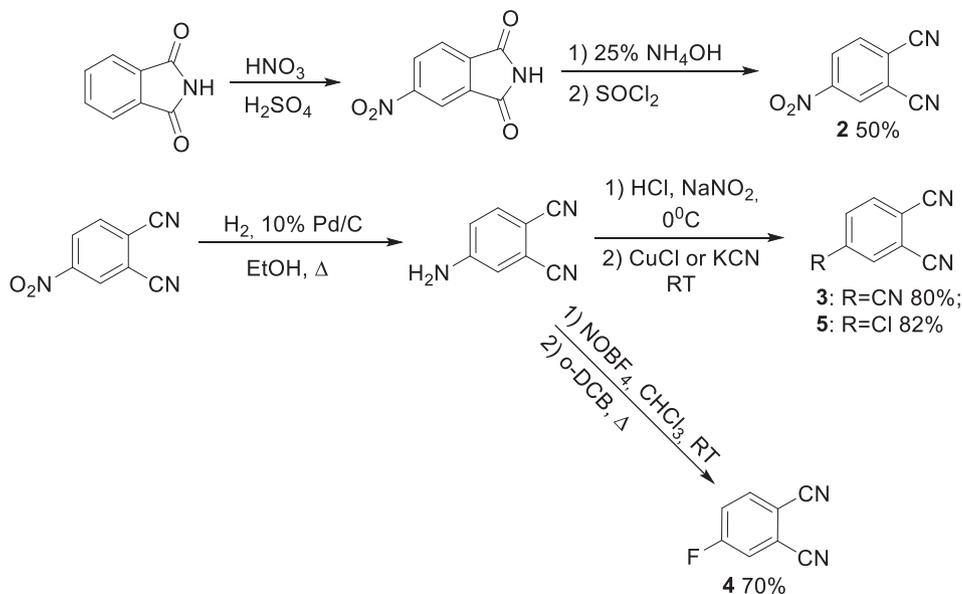
The formation of palladium complexes was confirmed by UV–Vis spectroscopy, ESI–HRMS mass spectrometry and ¹H NMR spectroscopy. UV–Vis spectrum of complexes **1** and **6–9** showed non-splitting Q and Soret band that is typically for phthalocyanine complexes. It should be noted that ¹H NMR spectra of phthalocyanine palladium complexes are complicated because they consist of mixture of regioisomers which are not separated by chromatography and HPLC. We observed proton signals of *tert*-butyl groups and aromatic phenyl rings in ¹H NMR spectrum.

The *m/z* values in the ESI–HRMS spectra confirm the structure of the complex and the isotopic distribution which is typical for such palladium complexes is in accordance with the calculated data.

The potential advantages of the novel catalyst system based on palladium complexes of phthalocyanines, the ease of separation and facile recycling of the catalyst and the absence of metal contamination in the product, suggest that an efficient Sonogashira coupling protocol based on the use of this catalyst system and utilizing aromatic halides other than iodides would be of major interest for both industrial and academic applications.

Herein, we report our results on the development of new catalytic systems based on palladium phthalocyanines and use in Sonogashira cross-coupling reaction of phenylacetylene with various *p*-substituted aryl bromides. First, we have investigated Pd/Cu-catalyzed Sonogashira reaction of bromobenzene with phenylacetylene as model substrates under various conditions. The reactions were performed in the presence of ^tBuPcPd catalysts, CuI as a co-catalyst, Et₃N as base and various solvents in test tubes of Radleys Carousel 6 plus at 25 °C and yields of products were determined by GC/MS. The reaction conditions explored are summarized in Table 1.

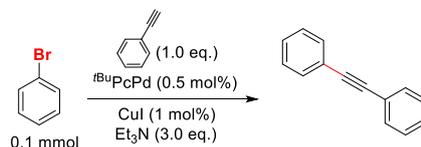
The first task of our investigation was to estimate of the influence of different reaction parameters on the catalytic activity in order to optimize the protocol. The limitations of this protocol have been tested in respect to catalyst, solvent and reaction time. Bases



Scheme 3. Synthetic pathway for preparation of phthalonitriles 2–5.

Table 1

Pd-catalyzed Sonogashira cross-coupling reaction of bromobenzene with phenylacetylene: Optimisation of reaction parameters.^[a]



Entry	Catalyst	Solvent	Time (h)	Yield (%) ^[b]	Yield (%) ^[b] without CuI	Yield (%) ^[b] of homocoupling product
1	^t BuPcPd	CH ₂ Cl ₂	8	98	72	Trace
2	^t BuPcNO ₂ Pd	CH ₂ Cl ₂	6	96	77	Trace
3	^t BuPcCNPd	CH ₂ Cl ₂	7	92	70	2
4	^t BuPcFPd	CH ₂ Cl ₂	8	90	68	4
5	^t BuPcClPd	CH ₂ Cl ₂	8	80	62	5
6	^t BuPcNO ₂ Pd	PhMe	8	15	Trace	10
7	^t BuPcNO ₂ Pd	MeCN	8	60	43	11
8	^t BuPcNO ₂ Pd	DMA	8	55	30	20
9	^t BuPcNO ₂ Pd	DMF	8	61	35	14
10	^t BuPcNO ₂ Pd	1,4-Dioxane	8	27	19	8
11	^t BuPcNO ₂ Pd	^t BuOH	8	77	59	9
12	^t BuPcNO ₂ Pd	CyH	8	18	Trace	10

^[a] All reactions were performed on 0.1 mmol scale in 2 ml anhydrous solvent in test tube.

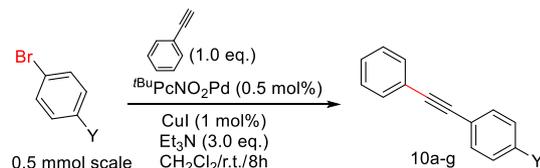
^[b] The conversion yield was determined by GC/MS based on the integration of peaks.

are known to play a major role and strongly influence catalytic activities in cross coupling reactions and we have focused on testing the protocol with use of triethylamine as base. It was found that catalysts based on palladium complexes of tetra-*tert*-butyl-substituted phthalocyanine **1** and unsymmetrical A₃B-type phthalocyanines containing NO₂⁻ and CN⁻ electron withdrawing groups have the highest catalytic activity among tested compounds. We synthesized desired product of cross-coupling reaction – diphenylacetylene with high yields (92–98%) in dichloromethane at room temperature with low loading of catalyst (Table 1, entries 1–3). We attempted to carry out Sonogashira reaction in other solvents and with use of different bases such as cesium carbonate, DBU, DABCO, potassium phosphate tribasic and revealed only low conversion of initial substrates (Table 1 and see Supporting information for details). It should also noted that we carried out catalytic investigations in order to determine the influence of

cocatalyst Cu(I) on yield of diphenylacetylene in Sonogashira cross-coupling (Table 1). Obtained results revealed that Pd-catalyzed reaction of phenylacetylene with bromobenzene without copper(I) iodide lead to decrease of product conversion that is associated with lowering of phenylacetylene reactivity.

Palladium complex **6** with nitro group showed highest catalytic activity among tested compounds in model Sonogashira reaction and it was chosen for using in synthesis diverse diphenylacetylenes **10a-g**. The results are summarized in Table 2.

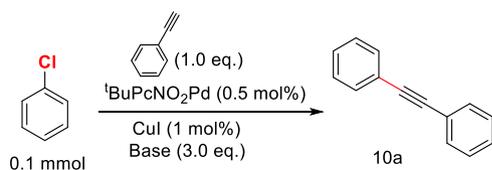
As expected, all of the arylalkynes were readily generated from the corresponding bromides and obtained in good yields without being contaminated with byproducts of homocoupling reacting such as dimer of phenylacetylene. Interestingly, the presence of functional groups at the *para*-position of aryl bromides did not influence on the yields of products (Table 2, entries 2–7).

Table 2Pd-catalyzed Sonogashira cross-coupling reaction of aryl bromides with phenylacetylene.^[a]

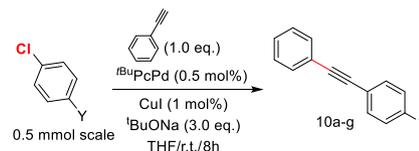
Entry	Aryl bromide	Product	Yield (%) ^[b]
1			98
2			95
3			94
4			91
5			90
6			93
7			89

^[a] All reactions were performed on 0.5 mmol scale in 5 ml anhydrous CH₂Cl₂ in test tube.^[b] Isolated yields.

Due to our excellent results of catalyst based on palladium *tert*-butyl-substituted phthalocyanine **6** in Sonogashira coupling of aryl bromides, then we have decided to investigate also the catalytic activity of this complex in the cross-coupling of the less reactive aryl chlorides with phenylacetylene. We have chosen the optimized conditions in case of reaction of *p*-substituted aryl bromides with phenylacetylene (substrate ratio (1:1), Et₃N, DCM, 25 °C) and applied in Pd/Cu-catalyzed coupling of aryl chlorides. It should be noted that the reaction in these conditions yielded mainly to by-

Table 3Pd-catalyzed Sonogashira cross-coupling reaction of chlorobenzene with phenylacetylene: Optimisation of reaction parameters.^[a]

Entry	Base	Solvent	Conversion (yield%) ^[b]	Yield (%) ^[b] of homocoupling product
1	<i>i</i> -Pr ₂ NEt	CH ₂ Cl ₂	Trace	20
2	Cs ₂ CO ₃	CH ₂ Cl ₂	No reaction	14
3	<i>i</i> -Pr ₂ NEt	THF	Trace	12
4	Cs ₂ CO ₃	THF	No reaction	17
5	<i>i</i> -Pr ₂ NEt	DMA	Trace	19
6	Cs ₂ CO ₃	DMA	No reaction	21
7	^t BuONa	THF	91 (86)	5
8	^t BuONa	1,4-Dioxane	85 (74)	9
9	^t BuONa	DMF	82 (78)	5
10	^t BuONa	DMA	79 (73)	4

^[a] All reactions were performed on 0.1 mmol scale in 2 ml anhydrous solvent in test tube.^[b] The conversion yield was determined by GC/MS based on the integration of peaks.**Table 4**Pd-catalyzed Sonogashira cross-coupling reaction of aryl chlorides with phenylacetylene.^[a]

Entry	Aryl chloride	Product	Yield (%) ^[b]
1			84
2			81
3			90
4			83
5			82
6			87
7			80

^[a] All reactions were performed on 0.5 mmol scale in 5 ml anhydrous CH₂Cl₂ in test tube.^[b] Isolated yields.

products of homocoupling of phenylacetylene and we have observed only traces of desired cross-coupling products, that can be associated with low reactivity of chlorobenzene. On the basis of obtained results we have attempted to selection of reaction conditions varying nature of solvent and temperature. The finding results are summarized in Table 3.

It was found that only nature and base strength plays major role in conversion of chlorobenzene to diphenylacetylene via palladium-catalyzed cross-coupling reaction. The most effective catalytic system was 0.5 mol % ^tBuPcNO₂Pd as catalyst, sodium *tert*-butoxide as base and tetrahydrofuran as solvent in synthesis of the desired compound diphenylacetylene (Table 3, entry 7). In several studies have shown effectiveness of sodium *tert*-butoxide as a base in Pd-catalyzed Sonogashira reaction and it was shown that application of strong base allow to decrease of reaction temperature and obtain coupling products with good yields [39,40]. It should be noted that common palladium catalyst (Pd(OAc)₂, Pd₂(dba)₃, Pd(PPh₃)₄) didn't catalyzed this transformation and we haven't detected products in GC/MS experiment.

With the optimized conditions for the formation of diphenylacetylene from chlorobenzene (Table 1, entry 1), we have examined the scope of the Sonogashira reaction for the synthesis of diverse alkyne-functionalized benzenes using various terminal alkynes. The results are summarized in Table 4.

3. Conclusion

In summary, we have successfully synthesized used the *tert*-butyl-substituted palladium phthalocyanines as novel efficient catalysts of Sonogashira coupling of the different *p*-substituted aryl bromides with phenylacetylene under mild conditions. We investigated influence of electron withdrawing groups on catalytic activity palladium complexes in cross-coupling reaction. It was also demonstrated for the first time that amino group in 4-bromoaniline doesn't participate in palladium-catalyzed C-N coupling with formation of bis(4-bromophenyl)amine. It should be noted that new catalytic system based on metal phthalocyanines

was very effective in cross-coupling reaction of substituted aryl chlorides with phenylacetylene in combination with sodium *tert*-butoxide as base in tetrahydrofuran at room temperature. Developed approach allows to prevent of palladium black formation (agglomeration of metal particles) that exclude escape of catalyst from reaction media and considerably increase of its efficiency in comparison with other palladium catalysts.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcat.2020.08.019>.

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