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Anthracen-9-ylmethylene-(4-methoxyphenyl)amine: efficient promoter for silver-free palladium-catalyzed aerobic oxidative Sonogashira reactions

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Abstract

An efficient protocol for the synthesis of unsymmetrical substituted diarylacetylenes by the C(sp^2)–C(sp) cross-coupling reactions of substituted phenylacetylenes and electronically different arylboronic acids has been developed. Anthracen-9-ylmethylene-(4-methoxyphenyl)amine was employed as an efficient promoter in this Pd(OAc)$_2$-catalyzed oxidative Sonogashira reaction in air in the absence of silver salt under optimized reaction conditions. The impact of reaction parameters such as solvent, base, reaction temperature and time in this silver-free aerobic oxidative Sonogashira cross-coupling reaction was also evaluated. Electron-deficient phenylacetylenes, which are sluggish coupling partners in the traditional Sonogashira reaction, underwent coupling in this protocol. The catalytic system is inexpensive, effortlessly attainable and highly flexible for functionalized phenylacetylenes and arylboronic acids.

Keywords Anthracene–Schiff base · Palladium-catalyzed · Silver-free · Oxidative Sonogashira coupling · Diarylacetylenes

Introduction

Disubstituted acetylene unit is a prevalent motif in numerous bioactive natural products [1–5], oligomers [6, 7], polymers [8, 9], dendrimers [10, 11], fine chemicals [12–15], optoelectronic materials [16–20], etc. The traditional palladium-catalyzed Sonogashira reaction of substituted phenylacetylene with organic halides (or pseudohalides) using copper(I) as co-catalyst has emanated as a compelling and straightforward method for the synthesis of arylated internal alkynes [21–29]. However, copper salts may lead to the formation of sensitive and potentially explosive copper acetylides and also may result in the formation of diynes by Glaser–Hay-type homo-coupling of terminal alkynes [30, 31], thereby reducing the product efficiency. In addition, Sonogashira reaction generally gives poor yields in the case of electron-deficient alkynes [32, 33]. Hence, the development of new catalytic systems and use of easily available inexpensive starting materials rather than organic halides by the modifications of the Sonogashira protocol have received considerable attention.

In recent years, transition metal-catalyzed oxidative coupling between functionalized arylboronic acids and terminal alkynes has emerged as a substitute for the traditional Sonogashira reaction. This carbon–carbon cross-coupling reaction has numerous advantages, such as mild reaction conditions, ease of preparation or commercial availability of many air- and water-stable derivatives of boronic acid, effortless handling techniques, straightforward removal of boron residues, non-lethal nature of reagents and by-products as well as high functional group tolerance, thus explaining the increasing interest in this methodology. Various research laboratories have reported iron- [34], nickel- [35, 36], copper- [37–41], palladium- [42–48] and gold-mediated oxidative Sonogashira coupling [49] of functionalized arylboronic acids with substituted terminal alkynes as an alternative approach for the traditional Sonogashira reaction. However, in order to improve the catalytic efficiency, expensive silver salt was generally used as an oxidant (additive) in most of the reported literature protocols. Although interesting results have been obtained, there is still a need for

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the development of a general and efficient catalytic system for the silver-free protocols for this transformation.

The present work accounts for the synthesis of diarylacetylenes by Pd(OAc)$_2$-catalyzed C(*sp*^{2})–C(*sp*) cross-coupling reactions of electronically different arylboronic acids and functionalized phenylacetylenes by employing anthracen-9-ylmethylene-(4-methoxyphenyl)amine (L) as promoter. The reaction was performed under aerobic conditions in the absence of any silver salt under optimized conditions of solvent, base and reaction temperature. Further, the use of anthracen-9-ylmethylene-(4-methoxyphenyl)amine as promoter in palladium-catalyzed oxidative Sonogashira reaction in the absence of any silver(I) salt as oxidant is unparalleled.

Experimental section

Materials and methods

All the chemicals used in this work were of analytical grade available commercially and were used as received. The simple and inexpensive anthracene-derived Schiff base was readily accessible in good yield by the condensation of *p*-anisidine with anthracene-9-carboxaldehyde (see ESI† Scheme S1) and characterized by single-crystal X-ray diffraction (Fig. S1) studies (Table S1) [15], FT-IR, NMR and MS (see ESI†). The FTIR spectra of schiff base were recorded as KBr pellets on PerkinElmer Spectrum RX I spectrophotometer. NMR spectra were obtained on a Bruker Avance III NMR 400 MHz spectrometer operating at room temperature. ESI mass spectra were recorded on Elmer Clarus 900 C GC–MS spectrometer.

Typical procedure for the oxidative coupling reaction

A mixture of arylboronic acid (1.0 mmol), phenylacetylene (1.2 mmol), Pd(OAc)$_2$ (1.0 mol%), L (1.0 mol%) and 1,8-diazabicycloundec-7-ene (DBU) (2.0 mmol) in DMF (5 mL) was stirred at 100 °C in air for 4 h. The reaction mixture was then diluted with EtOAc (20 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered and the solvent was removed. The residue was subjected to column chromatography on silica gel using ethyl acetate and *n*-hexane mixture to afford the desired product. The products were characterized by ^{1}H and ^{13}C NMR analysis.

Results and discussion

In view of the continuous effort to develop a new catalytic system for the synthesis of diarylacetylenes by oxidative Sonogashira cross-coupling reaction, the Pd(OAc)$_2$-catalyzed coupling reaction between phenylacetylene and phenylboronic acid to furnish 1,2-diphenylethyne was first selected as a model system for scrutinization. The reaction was performed in air using L as the promoter in the absence of silver salts, and various reaction parameters such as the solvent, base, temperature and time were varied progressively in order to determine the optimum conditions.

At the outset, to find a proper solvent which can accelerate the rate of the reaction, various solvents were screened using Pd(OAc)$_2$ in conjunction with L and 1,8-diazabicycloundec-7-ene (DBU) as base under aerobic conditions at 100 °C for 2 h. The extent of product formation was solvent dependent. Solvents of low polarity, such as 1,4-dioxane, toluene or xylene, resulted in low yields (up to 44%) of the desired product. Among the solvents screened, superior performance was observed in DMF with 78% yield. When other polar solvents such as DMSO, *N*,*N*-dimethylacetamide (DMA) or *N*-methylpyrrolidone (NMP) were employed, relatively lower but promising isolated yields of 73, 74 and 63% of the desired product was obtained. Poor yield (~ 8%) of the desired 1,2-diphenylacetylene was obtained in water, which may be as a result of the poor solubility of L in water. Therefore, DMF was considered as a suitable and effective solvent for the coupling reaction protocol.

In carbon–carbon cross-coupling reactions, base plays a decisive role, and the effects of different bases (DBU, pyridine, Bu$_3$N, Et$_3$N, K$_2$CO$_3$, KHCO$_3$ and K$_3$PO$_4$) were then investigated (Table 1, entries 1–7). Notable sensitivity to base used was noted using Pd(OAc)$_2$/L/DBU in air at 100 °C for 2 h. The results from the optimization of bases revealed that DBU had ranked the highest yield (78%) of the desired 1,2-diphenylacetylene (entry 1) and was the best choice among other bases screened. A negative impact on the product yield was observed upon lowering the reaction temperature with best yields at 100 °C (Table 1, entries 1, 8–10). In addition, controlled experiments established that in the absence of Pd(OAc)$_2$ or DBU, no detectable cross-coupling product was obtained (entries 11, 12). Further, though Pd(OAc)$_2$-DBU could catalyze the coupling reaction without L, the efficacy was poor with only 30% yield of the product (entry 13). Hence, it was inferred that L acted as an effective promoter in this coupling reaction. Gratifyingly, the protocol did not yield any homo-coupled products of either coupling partners. Also, unlike the prior reports on transition metal-catalyzed oxidative Sonogashira coupling, all reactions proceeded well using Pd(OAc)$_2$/L/DBU/DMF within a short reaction time even in the absence of any silver(I) salt as oxidant.

The formation of the desired 1,2-diphenylacetylene from the corresponding coupling partners as a function of time is also presented (Fig. 1). From the results, it was deduced that with the progress of the reaction time, the formation of the desired 1,2-diphenylacetylene increased initially and then reached a maximum before it remained unaltered. At an optimum reaction time of 2.5 h, a reasonably good isolated yield (90%) of the desired 1,2-diphenylacetylene was observed using $Pd(OAc)_2$/L/DBU/DMF in air. In addition to $Pd(OAc)_2$, the catalytic efficacy of various palladium compounds such as $PdCl_2$, $Pd(NO_3)_2$, $[Pd(PPh_3)_2Cl_2]$ and $Pd(PPh_3)_4$ in the oxidative Sonogashira coupling was then examined (Fig. 2). All the palladium compounds were found to be suitable catalysts for the reaction, with $Pd(OAc)_2$ being the best, and others were inferior to palladium acetate. $Pd(OAc)_2$ resulted in formation of 90% of the desired product in 2.5 h. However, in the same reaction time, $PdCl_2$ and $Pd(NO_3)_2$ yielded only 58% and 48%, respectively, in the same time. $[Pd(PPh_3)_2Cl_2]$ and $[Pd(AsPh_3)_2Cl_2]$ gave even lower yields of 22% and 18% under identical conditions. The observations could emphasize the advantages of using palladium acetate as catalyst.

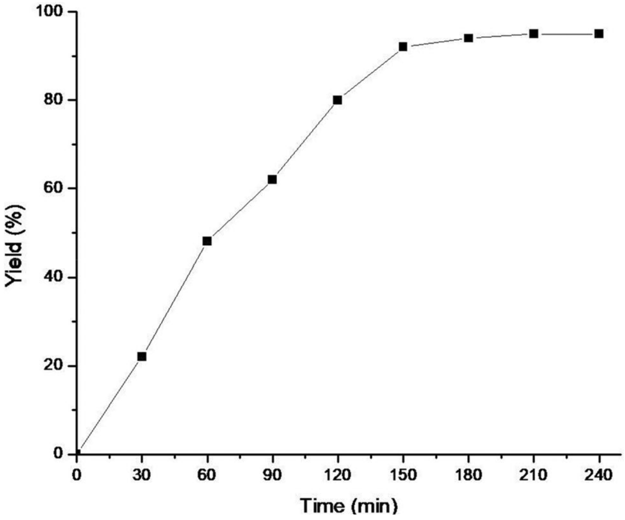
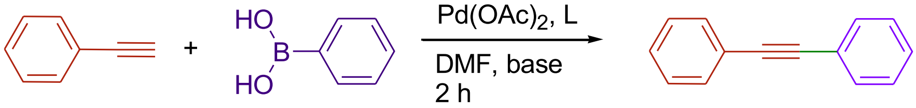


Fig. 1 Effect of reaction time using $Pd(OAc)_2$/L/DBU in air at 100 °C

The scope and feasibility of the above-mentioned optimized reaction conditions ($Pd(OAc)_2$, L, DMF, DBU, 100 °C, 2.5 h) were then employed for the oxidative coupling of phenylacetylene (as a representative terminal alkyne derivative) with functionalized aryl boronic acids containing

Table 1 Optimization of base and temperature



Entry	Base	Temp. (°C)	Yield[a] (%)
1	DBU	100	78
2	Pyridine	100	49
3	Bu_3N	100	65
4	Et_3N	100	63
5	K_2CO_3	100	36
6	$KHCO_3$	100	32
7	K_3PO_4	100	24
8	DBU	80	54
9	DBU	60	20
10	DBU	40	Trace
11	DBU[b]	100	Trace
12	–	100	Trace
13	DBU[c]	100	30

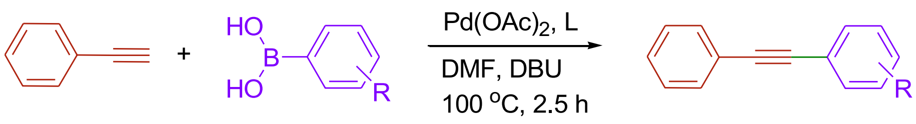
Phenylboronic acid (1.0 mmol), phenylacetylene (1.2 mmol), $Pd(OAc)_2$ (1.0 mol%), L (1.0 mol%), solvent (5 mL), base (2.0 mmol) in air for 2 h

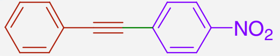
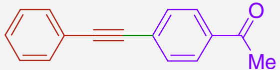
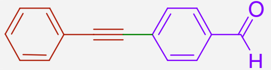
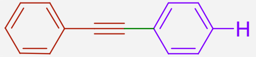
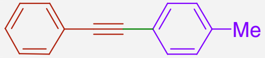
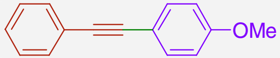
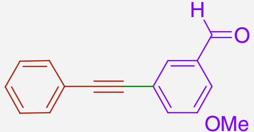
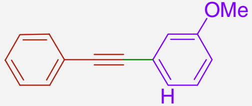
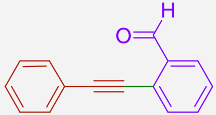
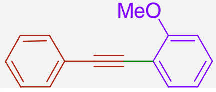
[a] Isolated yield after column chromatography (average of two independent runs)

[b] In the absence of $Pd(OAc)_2$

[c] In the absence of L

Table 2 C–C coupling reactions of phenylboronic acid with substituted phenylacetylene



Entry	Product	Yield (%)[a]
1		99
2		96
3		92
4		90
5		86
6		82
7		88
8		76
9		78
10		70

Reaction condition: Arylboronic acid (1.0 mmol), phenylacetylene (1.2 mmol), $Pd(OAc)_2$ (1.0 mol%), L (1.0 mol%), DMF (5 mL), DBU (2.0 mmol) at 100 °C in air for 2.5 h

[a] Isolated yield after column chromatography (average of two independent runs)

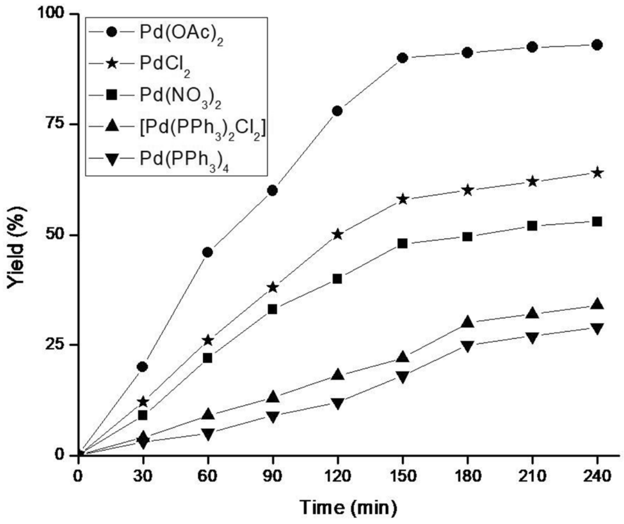
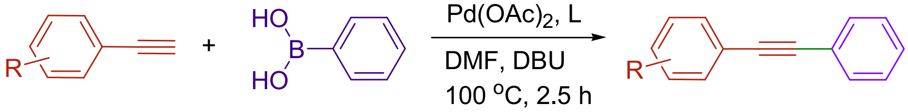
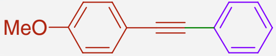
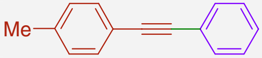
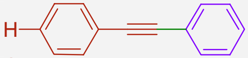
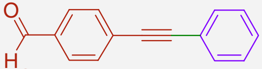
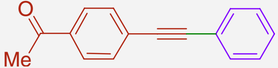
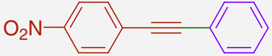
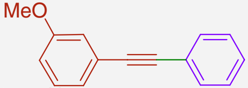
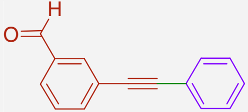
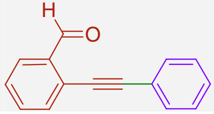


Fig. 2 Effect of various palladium compounds on reaction conversions

substituents (4-NO_2, 4-COMe, 4-CHO, 4-H, 4-Me, 4-OMe, 3-CHO, 3-OMe, 2-CHO, 2-OMe) of varying electronic and steric properties (Table 2). All the cross-coupling reactions were accomplished under similar reaction conditions for the facilitation of correlation of the results. It was inferred that the substituted arylboronic acids reacted easily with phenylacetylene to furnish the corresponding internal alkynes in good to excellent yields, when electron-withdrawing (4-nitro, 4-acetyl, 4-formyl), electron-neutral and electron-donating (4-methyl, 4-methoxy) substituents were present on the arylboronic acids. Fabulously, aryl boronic acids bearing electron-withdrawing groups (entries 1–3) afforded superior isolated yield of the desired product when compared with those having electron-donating groups (entries 5, 6). Utilization of 3-formylphenylboronic acid and 3-methoxyphenylboronic acid as coupling partners (entries 7, 8) in this reaction resulted in the formation of the corresponding

Table 3 C–C coupling reactions of phenylboronic acid with substituted phenylacetylene



Entry	Product	Yield (%)[a]
1		98
2		95
3		90
4		88
5		85
6		82
7		88
8		76
9		78
10		70

Reaction condition: Phenylboronic acid (1.0 mmol), arylacetylene (1.2 mmol), Pd(OAc) (1.0 mol%), L (1.0 mol%), DMF (5 mL), DBU (2.0 mmol) at 100 °C in air for 2.5 h

[a]Isolated yield after column chromatography (average of two independent runs)

desired products with high yields up to 88%. Gratifyingly, employment of 2-formylphenylboronic acid and 2-methoxyphenylboronic acid (entries 9, 10) resulted in slightly reduced yields than for the corresponding para-derivatives (entries 1, 5). The decline in the reaction yield may be a result of the steric effects enforced by the substituents in the ortho-position, hindering coordination of the substrate to the palladium centre. To our delight, under the given conditions, the homo-coupling by-products of neither the phenylacetylene nor the arylboronic acid were detected.

Additional coupling reactions were then carried out in an inverted manner, i.e., with functionalized phenylacetylenes and phenylboronic acid (as a representative arylboronic acid) to establish the scope and feasibility of different phenylacetylenes (Table 3). All of these reactions also gave the desired products in good-to-excellent isolated yields. It was deduced that the substituted phenylacetylenes coupled smoothly with arylboronic acids to yield the corresponding internal alkynes in good-to-excellent yields. Phenylacetylenes bearing electron-donating groups (such as 4-methoxy or 4-methyl) afforded greater isolated yield of the desired product when compared with those having electron-withdrawing groups (such as 4-formyl, 4-acetyl or 4-nitro). Utilization of 3-ethynylanisole and 3-ethynylbenzaldehyde as coupling partners (entries 7, 8) in this reaction resulted in isolated yields comparable to that of the corresponding para-substituted derivatives (entries 1, 4). However, as expected due to steric effects, 2-ethynylanisole and 2-ethynylbenzaldehyde (entries 9, 10) resulted in slightly inferior yields than for the corresponding para-substituted derivatives (entries 1, 4).

The salient features of this protocol included simple and convenient reaction procedure, insensitivity toward air and moisture, ease of handling of the reagents, lower reaction time, broad substrate scope and simple work-up procedure. In addition, the reaction gives good yields with electron-deficient alkynes, a system where traditional Sonogashira reaction gives poor yields. Further, though there are a few reports on the palladium-catalyzed oxidative Sonogashira reactions, a direct comparison of the present catalytic system with those reported earlier is difficult due to the differences in the reaction conditions such as solvent, base, temperature, reaction time and catalyst loading. However, in the absence of any silver additive, in terms of isolated yields or reaction time, the catalytic efficiency of the present protocol was found to be comparable or even slightly superior to some of the previous reports on palladium-catalyzed oxidative Sonogashira coupling reaction [42–48].

Conclusions

We developed a new protocol using Schiff base derived from anthracene as promoter for the palladium-catalyzed synthesis of internal alkynes by the carbon–carbon coupling reactions between functionalized arylboronic acids with substituted phenylacetylenes. The protocol worked well for substrates possessing electron-donating and electron-withdrawing substituents. The desired products were obtained in satisfactory-to-excellent isolated yields. This protocol provides the first example of anthracen-9-ylmethylene-(4-methoxy-phenyl)-amine as effective promoter for palladium-catalyzed oxidative Sonogashira cross-coupling reaction in the absence of any Ag(I) salts as oxidant. In addition, electron-deficient substituted phenylacetylenes also coupled well using this protocol. Further, scope, mechanism and synthetic applications of this catalytic reaction are under investigation in our laboratory.

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Compliance with ethical standards

Conflict of interest There are no conflicts to declare.

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