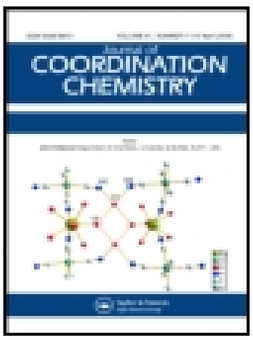

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New palladium-*bis*(oxazoline)-phosphine complexes: synthesis, characterization and catalytic application in alkoxycarbonylation of alkynes

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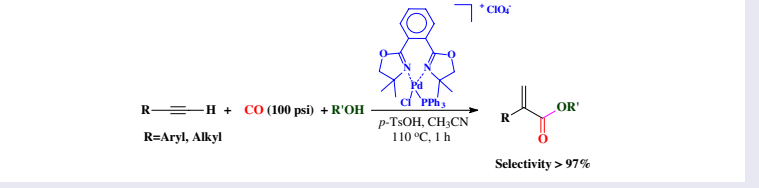
ABSTRACT

New cationic palladium-*bis*(oxazoline)-phosphine (Pd-BOX-PR_3) complexes (Pd-BOX-B and Pd-BOX-C) have been synthesized and characterized using ^{1}H, ^{13}C and ^{31}P NMR, FTIR spectroscopy, and electrospray ionization mass spectrometry (ESI-MS). The new complexes were used as catalysts in the alkoxycarbonylation of alkynes with various alcohols as nucleophiles. The carbonylation has produced the *gem*-*α*,*β*-unsaturated ester isomer (**3**) in high regioselectivity and excellent yields. The catalyst systems have been optimized by screening the type of palladium complexes and also by varying the reaction parameters including the reaction time, solvent, and temperature. A mechanism of the catalytic cycle based on a N-protonated palladium *bis*(oxazoline) phosphine active species was proposed for the alkoxycarbonylation reaction.



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Palladium; *bis*(oxazoline); alkoxycarbonylation; activity; selectivity

1. Introduction

Palladium-catalyzed carbonylation of alkynes in the presence of alcohol or amine as a nucleophile represents a major industrial process for the production of value-added bulk and fine chemicals. It is a versatile synthetic pathway to a wide range of linear, branched and cyclic *α*,*β*-unsaturated carboxylic acids, amides and their derivatives in one step and from easily accessible starting materials [1–5]. The carboxamides and cinnamate esters produced from the above reactions are used as building blocks for various materials ranging from polymers [6], light-sensitive, and electrically conductive materials, detergents, flavors, fragrances, and various pharmaceuticals [7].

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A highly active and selective catalyst is necessary for a successful carbonylation reaction. Palladium complexes are the most efficient catalysts for alkoxycarbonylation reactions, attributed to their high activity under mild conditions. Most of the catalytic systems used in carbonylation reactions are generated in situ from a palladium salt, a phosphine ligand, and a weakly coordinating acid [3, 8, 9]. Various catalytic systems [10–12] have been used in the carbonylation of alkynes at low CO pressure. However, many systems are associated with relatively low activity and often give a mixture of products.

As continuation of our interest in exploring the synthesis, structural chemistry, and catalytic activity of palladium-*bis*(oxazoline) complexes [13–15], we report in this paper the synthesis, characterization, and catalytic activity of new palladium-*bis*(oxazoline)-phosphine (Pd-BOX-PR_3) complexes. Although a number of mixed ligand complexes of nitrogen and phosphine donors have been reported [16–19], the presence of the BOX as a chelating nitrogen ligand added more stability and catalytic activity to the complexes as demonstrated in our previous studies in coupling reactions [13–15]. The presence of phosphine was mandatory for the carbonylation reactions. The complexes described in this paper are the first examples of cationic mixed ligand palladium complexes having both *bis*(oxazoline) and phosphine. Palladium *bis*(oxazoline) complexes are rarely studied as catalysts in carbonylation reactions [20]. This encouraged us also to investigate the catalytic activity of our newly synthesized palladium complexes in the alkoxycarbonylation of various alkynes. The catalyst systems have been optimized by screening the types of phosphine ligand and also by varying the reaction parameters including the reaction time, solvent, and temperature.

2. Experimental

2.1. Materials

Materials for the synthesis of ligands and complexes were purchased from Sigma–Aldrich Company and used as received. All solvents (reagent grade) used in the synthesis were distilled and dried before use. The products were purified using flash column chromatography packed with Silica gel 170–400 Mesh, Fisher chemical (Fisher Scientific, US). Merck 60 F_{254} silica gel plates (250 µm layer thickness) were used for thin layer chromatography (TLC).

2.2. Instrumentation

^{1}H, ^{13}C, and ^{31}P NMR spectral data were obtained using 500 MHz NMR (Jeol 1500 model). Chemical shifts were recorded in ppm using tetramethylsilane (TMS) as reference for ^{1}H and ^{13}C spectra and phosphoric acid as reference for ^{31}P spectrum. CD_2Cl_2 was used as NMR solvent. IR spectra were recorded in wavenumbers (cm^{-1}) using a FTIR spectrometer (Perkin-Elmer 16F model). A Varian Saturn 2000 GC-MS machine equipped with a 30 m capillary column was used to analyze the products. Agilent 6890 Gas chromatograph (GC) was used to monitor the reactions and analyze the products. Molecular weight analyses of the complexes were performed on an LTQ-Orbitrap mass spectrometer (Thermo Scientific, San Jose, CA, USA) equipped with a HESI-II electrospray source (ESI-MS) using a metal spray needle.

2.3. Synthesis of palladium-bis(oxazoline) complex (Pd-BOX-A) [13]

A solution of *bis*(oxazoline) ligand A (0.5 mmol) and *bis*(benzonitrile) palladium(II) chloride (0.5 mmol) in dried DMF (8.0 mL) was stirred at room temperature for 6 h. The solvent was removed under reduced pressure using a rotary evaporator. The crude product was then dissolved in dichoromethane at room temperature and layered with hexane. The product was obtained as needles. These pure crystals were separated, washed with diethyl ether, dried under vacuum, and characterized using different spectroscopic techniques including ^{1}H and ^{13}C NMR, elemental analysis, IR spectroscopy, and X-ray diffraction analysis.

2.3.1. 2,2′-(1,2-phenylene)bis(4,4-di-methyl-4,5-dihydrooxazole)-N,N′-dichloridopalladium(II) (Pd-BOX-A)

Pale yellow needle shape crystals; yield (81%); m.p. (252 °C), ^{1}H NMR (500 MHz, DMSO) δ (ppm): 7.95 (m, 4H, C*H*-3,4,5,6 arom), 4.39 (s, 4H, OCH_2×2), 1.52 (s, 6H, NC(CH_3)$_2$), 1.57 (s, 6H, NC(CH_3)$_2$, ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm); 27.8 (NC(*C*H_3)×4), 70.8 (N*C*), 80.5 (O*C*H_2), 125.5 (C-1,2 arom), 129.5 (C-3,4 arom), 132.9 (C-5,6 arom), 163.9.(OCN); IR (KBr) (*vcm*$^{-1}$): 2968, 1632, 1260, 1193. Anal. Calcd for $C_{16}H_{20}Cl_2N_2O_2Pd$ (449.67): C, 42.74; H, 4.48; N, 6.23. Found: C, 42.71; H, 4.46; N, 6.29%.

2.4. Synthesis of palladium-bis(oxazoline)-phosphine complexes

To a stirred solution of Pd-BOX-A (0.25 mmol) in 10 mL dichloromethane, a stoichiometric amount of phosphine (0.25 mmol) (dissolved in 2 mL of dichloromethane) was added. The resulting mixture was stirred for 30 min at room temperature. Subsequently, the solvent was removed using a rotary evaporator at reduced pressure. The resulting solid product was dissolved in DMF (5 mL). A stoichiometric amount (0.25 mmol) of silver perchlorate ($AgClO_4$) was added and the mixture was stirred in the dark for 30 min. After complete reaction, the mixture was filtered to remove the AgCl precipitate. The solvent was removed under reduced pressure to give the appropriate mixed ligand palladium complex. The product was dissolved in dichloromethane and layered with *n*-hexane in an attempt to obtain pure microcrystals. The products were characterized using various spectroscopic and analytical techniques and the molecular weights were established on the basis of ESI-MS analyses.

2.4.1. Chlorido (2,2′-(1,2-phenylene)bis(4,4′-dimethyl-4,5-dihydrooxazole)-N,N′) triphenylphosphino palladium(II) perchlorate (Pd-BOX-B)

Yellow solid; yield: 72%; m.p. 230 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm): 8.11 (d, *J* = 7.6 Hz, 1H, C*H* arom), 8.00 (m, *J* = 5.2 Hz, 1H, C*H* arom), 7.81 (d, *J* = 3.05 Hz, 2H, C*H* arom), 7.56 (m, 3H, C*H* arom), 7.46 (m, 12H, C*H* arom), 4.51 (d, *J* = 8.85 Hz, 1H, OC*H*), 4.40 (d, *J* = 8.85 Hz, 1H, OC*H*), 4.33 (d, *J* = 8.85 Hz, 1H, OC*H*), 3.49 (d, *J* = 8.85 1H, OC*H*), 1.73 (s, 3H, NCCH_3), 1.66 (s, 3H, NCCH_3), 1.49 (s, 3H, NCCH_3), 0.73 (s, 3H, NCCH_3); ^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm): 24.35 (NC*C*H_3), 27.81 (NC*C*H_3), 29.46 (NC*C*H_3), 31.20 (NC*C*H_3), 71.47 (N*C*), 72.66 (N*C*), 81.25 (O*C*H_2), 82.44 (O*C*H_2), 125.37, 127.53, 128.54, 129.16, 130.08, 131.11, 132.46, 132.48, 133.47, 134.28, 134.70, 165.98, 166. ^{31}P NMR (500 MHz, CD_2Cl_2) δ (ppm); 21.34 (*P*Ph_3); IR (KBr) (*vcm*$^{-1}$): 3043, 2974, 2914, 2356, 1626, 1442, 1373, 1324, 1093, 949, 750, 701, 622, 527; ESI-MS: 676.12; Anal. Calcd for $C_{34}H_{35}Cl_2N_2O_6PPd$ (775.95): C, 52.63; H, 4.55; N, 3.61. Found: C, 52.41; H, 4.49; N, 3.60%.

2.4.2. Chlorido(2,2′-(1,2-phenylene)bis(4,4′-dimethyl-4,5-dihydrooxazole)-N,N′)tris(p-methoxy phenylphosphino) palladium(II) perchlorate (Pd-BOX-C)

Yellow solid, yield: 69%; m.p. 215 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm): 8.08 (d, *J* = 7.9 Hz, 1H, C*H* arom), 7.97 (m, 1H, C*H* arom), 7.82 (d, *J* = 3.7 Hz, 2H, C*H* arom), 7.35 (m, 6H, C*H* arom), 6.91 (m, 6H, C*H* arom), 4.48 (d, *J* = 8.6 Hz,1H, OC*H*), 4.39 (d, *J* = 8.8 Hz, 1H, OC*H*), 4.30 (d, *J* = 8.6 Hz, 1H, OC*H*), 3.84 (s, 9H, OCH_3), 3.56 (d, *J* = 9.2 Hz, 1H, OC*H*), 1.73 (s, 3H, NCCH_3), 1.65 (s, 3H, NCCH_3), 1.48 (s, 3H, NCCH_3), 0.81 (s, 3H, NCCH_3), ^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm); 24.37 (NC*C*H_3), 27.74 (NC*C*H_3), 29.40 (NC*C*H_3), 30.98 (NC*C*H_3), 55.98 (O*C*H_3), 71.42 (N*C*), 80.90 (O*C*H_2), 82.29 (O*C*H_2), 114.61, 114.71, 114.84, 120.23, 130.13, 131.05, 133.41, 134.16, 136.20, 136.30, 136.42, 162.76, 162.96; ^{31}P NMR (500 MHz, CD_2Cl_2) δ (ppm); 18.87 [(*p*-MeO-C_6H_4)$_3$*P*]; IR (KBr) (*vcm*$^{-1}$) 3062, 2973, 2840, 1897, 1634, 1592, 1567, 1500, 1458, 1407, 1373, 1292, 1260, 1180, 1096, 1020, 942, 828, 800, 717, 623, 541; ESI-MS: 765.15; Anal. Calcd for $C_{37}H_{42}Cl_2N_2O_9PPd$ (867.03): C, 51.25; H, 4.88; N, 3.23. Found: C, 51.42; H, 4.76; N, 3.40%.

2.5. General procedure for the alkoxycarbonylation of alkynes

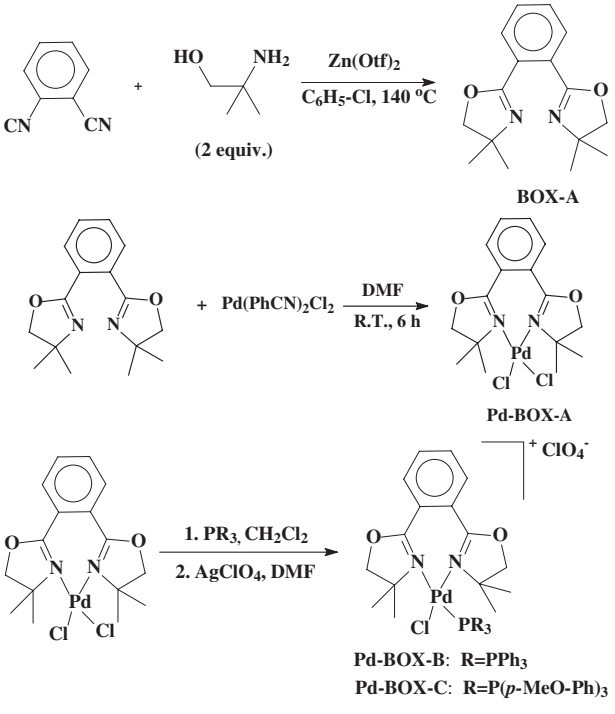
A stainless steel autoclave equipped with a glass liner, gas inlet valve, and pressure gage was used for the alkoxycarbonylation reaction. Pd-BOX-PR$_3$ (0.02 mmol) dissolved in 2 mL acetonitrile, *p*-toluenesulfonic acid

(*p*-TsOH) (0.30 mmol), alkyne (2.0 mmol), and alcohol (8.0 mmol) were added to the glass liner. Additional acetonitrile (8 mL) was added to the mixture in the glass liner. The glass liner was then placed in the 45 mL autoclave. The autoclave was vented three times with carbon monoxide and then pressurized to 100 psi of CO. The mixture was heated to 110 °C and maintained at this temperature under stirring for the required time. After complete reaction, the mixture was cooled to room temperature and excess CO was released in a fume hood. The mixture was filtered and the filtrate was immediately analyzed with GC and GC-MS [7]. The spectral data of the *α,β*-unsaturated esters prepared in this study were in agreement with those reported [21–24].

3. Results and discussion

3.1. Synthesis of BOX ligand, Pd-bis(oxazoline) dichloro (Pd-BOX-A) and Pd-bis(oxazoline)-chloro phosphine (Pd-BOX-B and Pd-BOX-C) complexes

The BOX ligand and Pd-BOX-A complex were prepared following the method reported [13] (scheme 1). Pd-BOX-B and Pd-BOX-C were obtained by introducing the appropriate phosphine to Pd-BOX-A. ^{1}H and ^{13}C NMR chemical shifts for both the BOX ligand and Pd-BOX-A were consistent with the reported structure. The BOX ligand is a symmetrical molecule, hence the two oxazoline moieties behave similarly: a single peak was observed for the methyl protons with a chemical shift of δ 0.88 ppm, integrating for 12 protons. The six methylenic protons are a singlet with chemical shift of δ 3.55 ppm (figure 1(a)) [12]. In the spectrum of palladium BOX complex (Pd-BOX-A), both the methyl and methylene protons were deshielded and were observed in the downfield region due to complexation with palladium. Unlike the spectrum of the free ligand, the two oxazoline moieties behave differently. Two singlets were observed in the methyl region, each integrating for six protons. The methylenic protons appear as two separate AB spin systems, with each doublet integrating for two protons (figure 1(b)) [12]. In



Scheme 1. Synthesis of BOX ligand, palladium *bis*(oxazoline) dichloro complex (Pd-BOX-A) and palladium *bis*(oxazoline) chloro phosphine complexes (Pd-BOX-B and Pd-BOX-C).

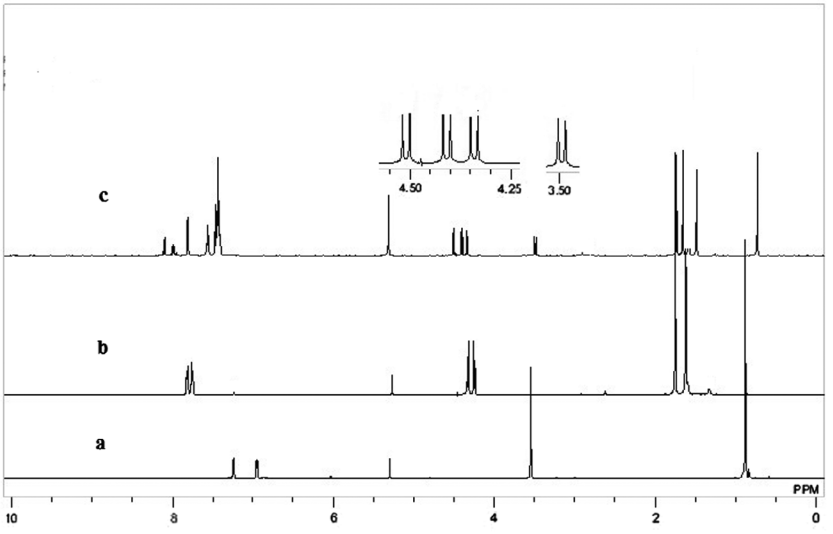


Figure 1. ^{1}H NMR spectra of (a) BOX ligand, (b) Pd-BOX-A, and (c) Pd-BOX-B.

spectra of Pd-BOX-phosphine complexes (Pd-BOX-B and Pd-BOX-C), there is further splitting of both the methyl and methylenic protons due to complete loss of symmetry in the molecules (scheme 1). In the spectrum of Pd-BOX-B four singlets were observed in the methyl region (figure 1(c)) with each singlet integrating for three protons. One of the four singlets is further upfield as opposed to the three remaining singlets which resonate at nearly the same chemical shift as in Pd-BOX-A. The methylenic protons are four different doublets integrating for one proton each (figure 1(c)). Similar to the methyl protons, one of the four doublets is further upfield, which is probably due to the anisotropic shielding of these protons by one of the phenyl rings of PPh_3 [25]. The protons, due to the aromatic spacer of the BOX and the aromatic phosphines, are in the aromatic region and slightly downfield as compared to their positions in the free state. The proton NMR spectrum of Pd-BOX-C shows a similar pattern to the spectrum of Pd-BOX-B with additional singlet at δ 3.84 ppm which was assigned to the *p*-methoxy substituent.

The carbon-13 NMR spectra for the BOX ligand, Pd-BOX-A, Pd-BOX-B, and Pd-BOX-C were consistent with the proposed structures and were in agreement with the spectra of other known BOX ligands and Pd-BOX complexes [13–15]. For instance, in the NMR spectrum of Pd-BOX-B and Pd-BOX-C, two sets of carbon signals were detected in the aromatic region. The weak signals represent the benzene spacer of the BOX ligand and the intense signals represent the triphenylphosphine and *p*-methoxy triphenylphosphine ligands for Pd-BOX-B and Pd-BOX-C, respectively. A downfield shift was observed in the resonance of the imino carbon (–C=N-) in spectra of Pd-BOX-A, Pd-BOX-B, and Pd-BOX-C. This shift is due to the increase in double bond character of the –*C*=*N*- bond as a result of coordination, which results in its deshielding.

Similarly, in the ^{31}P NMR spectra, the phosphorus resonances shifted from –6.0 and –11.8 ppm in the free ligands to δ 21.3 and 18.9 ppm for Pd-BOX-B and Pd-BOX-C, respectively. These shifts are further confirmation that the phosphine ligands are coordinated to form the mixed ligand complexes.

We recently published the crystal structure of Pd-BOX-A [13]. Attempts to grow crystals of Pd-BOX-B and Pd-BOX-C were not successful. We considered ESI-MS as a suitable technique to establish the molecular weight of our new mixed ligand complexes [26, 27]. Fortunately, the molecular weights obtained were in agreement with the calculated molecular weights (figures 2 and 3). These results together with

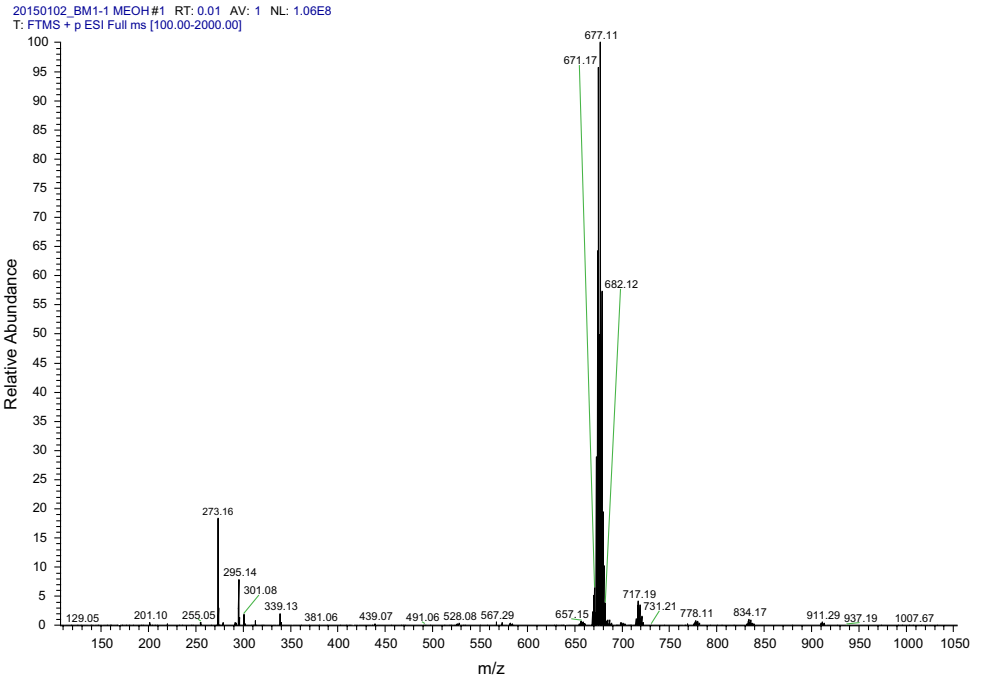


Figure 2. Proposed formulation for Pd-BOX-B based on isotope simulation and distribution is $[C_{34}H_{35}ClN_2O_2PPd]^+$ with $m/z = 676.12$.

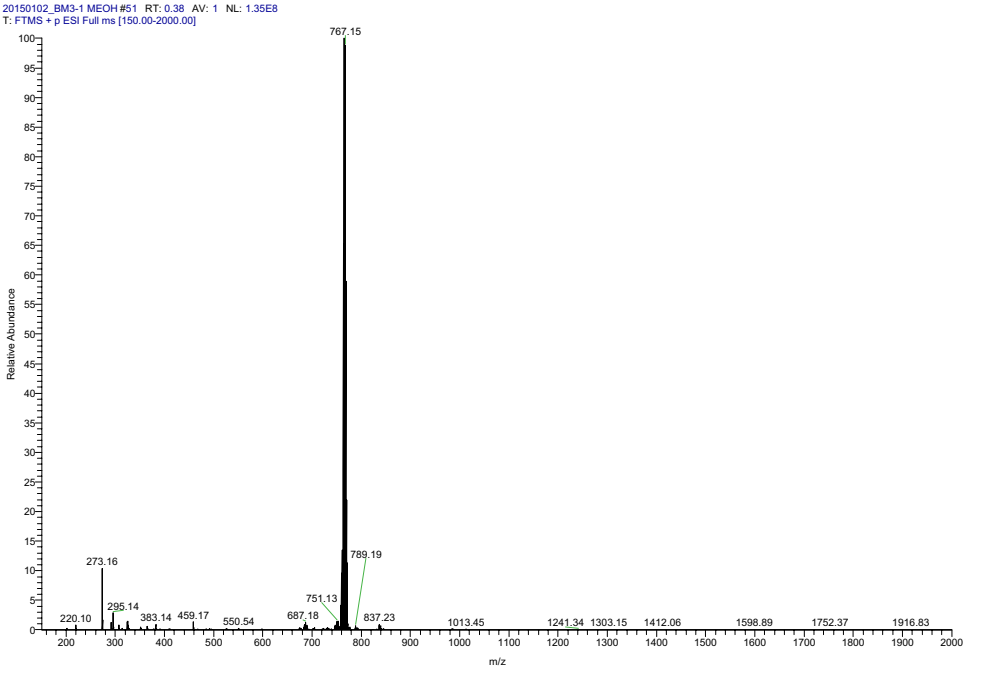


Figure 3. Proposed formulation for Pd-BOX-C based on isotope simulation and distribution most likely is $[C_{37}H_{41}ClN_2O_5PPd]^+$ with $m/z = 765.15$.

the information acquired from other spectroscopic techniques were used to establish the molecular structures of the new complexes (scheme 1).

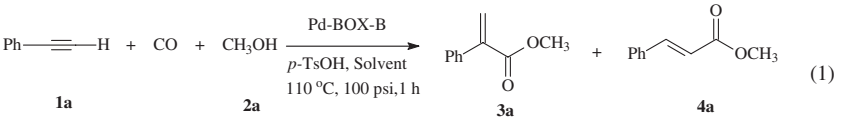
3.2. Evaluation of the catalytic activity of the newly prepared Pd-BOX complexes in the alkoxycarbonylation of alkynes

The reaction of terminal alkynes with alcohol in the presence of carbon monoxide as carbonyl source (alkoxycarbonylation) is a well-known methodology for the synthesis of *α,β*-unsaturated esters. In our investigation, we have chosen the methoxycarbonylation of phenylacetylene (**1a**) using Pd-BOX as a catalyst as a model reaction. Two *α,β*-unsaturated ester isomers, *gem* (**3aa**) and *trans* (**4aa**), are expected as products from this reaction. We have studied the influence of various reaction parameters including solvent, temperature, and type of palladium catalyst.

A preliminary alkoxycarbonylation reaction of phenylacetylene with methanol (**2a**) using the catalyst system Pd-BOX-A/*p*-TsOH yielded only trace amounts of products. The in situ introduction of triphenylphosphine as a co-ligand resulted in higher catalytic activity and improved the conversion of phenylacetylene. This shows that the presence of a coordinated phosphine is necessary for the alkoxycarbonylation reaction.

3.2.1. Effect of solvent

We have investigated the effect of various solvents on the catalytic activity and selectivity of the model reaction using Pd-BOX-B/*p*-TsOH catalyst system. A complete conversion and excellent selectivity towards the formation of the *gem* isomer **3aa** were achieved with acetonitrile as a solvent (Table 1, entry 1). The conversion of the alkyne and the selectivity in *gem* isomer have decreased to 43 and 75%, respectively, when DMF was used as a solvent (Table 1, entry 2). A further decrease in the conversion of phenylacetylene to 28% was observed with *n*-hexane as a solvent, with a selectivity of 90% in favor of **3aa** isomer (Table 1, entry 3). Poor conversion and poor selectivity were observed when the reaction was performed in neat methanol (Table 1, entry 5). The coordination of anions to the cationic palladium center is reported to be very weak in non-polar solvents [28]. The reaction for higher activity of the alkoxycarbonylation reaction in acetonitrile is not yet understood but it is possible that this solvent plays the dual role of solvent and a co-ligand in the catalytic cycle [7, 8].



(1)

3.2.2. Effect of temperature

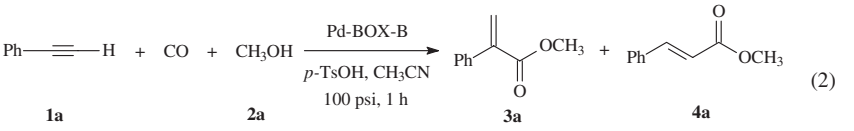
After determining the best solvent for the reaction, we have studied the effect of varying the temperature on the conversion and the selectivity of the methoxycarbonylation reaction of phenylacetylene using the catalytic system Pd-BOX-B/*p*-TsOH/CH_3CN. The catalytic activity was highly temperature

Table 1. Effect of the type of solvent on the palladium-catalyzed methoxycarbonylation of phenylacetylene.[a]

			Product distribution[b] (%)	
Entry	Solvent	Conversion[b] (%)	**3a**	**4a**
1	Acetonitrile	99	97	3
2	DMF	43	75	25
3	*n*-Hexane	28	90	10
4	Toluene	65	92	8
5	Methanol	10	65	35

[a]Reaction conditions: Pd-BOX-B (0.020 mmol), *p*-TsOH (0.30 mmol), solvent (10 mL), phenylacetylene (2.0 mmol), methanol (8.0 mmol), CO (100 psi), 110 °C, 1 h.
[b]Determined by GC based on phenylacetylene.

dependent. The conversion dropped significantly from 99 to 40% when the temperature was lowered from 110 °C (Table 2, entry 5) to 60 °C (Table 2, entry 1) and decreased to 70% at 90 °C (Table 2, entry 3). The selectivity was not affected by changing the reaction temperature.



(2)

Table 2. Effect of the temperature on the palladium-catalyzed methoxycarbonylation of phenylacetylene.[a]

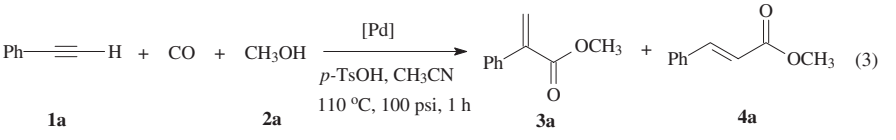
			Product distribution[b] (%)	
Entry	Temperature (°C)	Conversion[b] (%)	**3a**	**4a**
1	60	40	95	5
2	70	58	94	6
3	90	70	98	2
4	100	90	98	2
5	110	99	97	3

[a]Reaction conditions: Pd-BOX-B (0.020 mmol), *p*-TsOH (0.30 mmol), acetonitrile (10 mL), phenylacetylene (2.0 mmol), methanol (8.0 mmol), CO (100 psi), 1 h.
[b]Determined by GC based on phenylacetylene.

3.2.3. Effect of the type of palladium complex

The presence of a catalyst is essential for the progress of carbonylation reactions. Palladium complexes catalyze carbonylation reactions, however, the efficiency and selectivity in such reactions depend strongly on the type of palladium precursor, the attached ligand, and other reaction parameters.

The effect of the type of palladium complex and the ligand on the methoxycarbonylation of phenylacetylene was investigated. The results are summarized in Table 3. Only traces of products were observed with Pd-BOX-A as catalyst. There was a remarkable increase in the product yield (from traces to 75%) when triphenylphosphine was used as a co-ligand (Table 3, entries 2 and 3). The mixed ligand palladium complexes (Pd-BOX-B and Pd-BOX-C) (Table 3, entries 4 and 5) gave full conversion with 97 and 98% selectivity, respectively, towards **3aa**. To highlight more the activity of our newly prepared complexes, we have compared them with commercially available palladium complexes and salts such as $Pd(PPh_3)_2Cl_2$ (Table 3, entry 6) (54%), $Pd(PhCN)_2Cl_2$ (Table 3, entry 7) (traces), $Pd(OAc)_2$ (Table 3, entry 8) (traces), and $Pd(OAc)_2/PPh_3$ (Table 3, entry 9) (74%). The low catalytic activity or the inactivity observed with most commercial palladium complexes and salts is an indication of the significance of the new mixed ligand complexes on the alkoxycarbonylation reaction. The catalytic activity achieved with the new mixed ligand complexes is higher than the activity of the individual complexes combined (Pd-BOX-A and $Pd(Ph_3)_2Cl_2$) and is a clear indication of a synergistic relationship between the donor nitrogen and phosphorus ligands.



(3)

Table 3. Effect of the type of palladium catalyst on the methoxycarbonylation of phenylacetylene.[a]

			Product distribution[b] (%)	
Entry	Catalyst	Conversion[b] (%)	**3a**	**4a**
1	Pd-Box-A	Traces	–	–
2[c]	Pd-Box-A/PPh_3	75	90	10
3[d]	Pd-Box-A/PPh_3	90	90	10
4	Pd-Box-B	99	97	3
5	Pd-Box-C	99	98	2
6	$Pd(PPh_3)_2Cl_2$	54	92	8
7	$Pd(PhCN)_2Cl_2$	Traces	–	–
8	$Pd(OAc)_2$	Traces	–	–
9[d]	$Pd(OAc)_2$/PPh_3	74	95	5

[a]Reaction conditions: [Pd] (0.020 mmol), *p*-TsOH (0.3 mmol), acetonitrile (10 mL), phenylacetylene (2.0 mmol), methanol (8.0 mmol), CO (100 psi), 110 °C, 1 h.
[b]Determined by GC based on phenylacetylene.
[c]0.02 mmol PPh_3 was added.
[d]0.04 mmol PPh_3 was added.

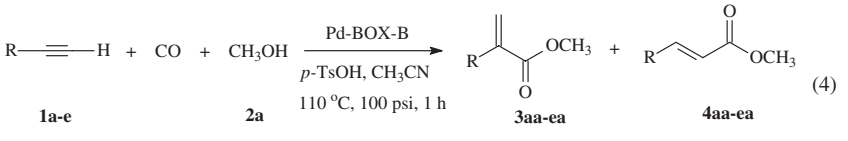
Table 4. Palladium catalyzed alkoxycarbonylation of phenylacetylene with various alcohols.[a]

			Product distribution[b] (%)	
Entry	Alcohol	Conversion[b] (%)	**3aa-ag**	**4aa-ag**
1	Methanol **2a**	99	97	3
2	Ethanol **2b**	99	98	2
3	Propanol **2c**	99	97	3
4	Butanol **2d**	99	96	4
5	Isopropanol **2e**	99	96	4
6	Isobutanol **2f**	99	97	3
7	Isopentanol **2 g**	99	97	3

[a]Reaction conditions: Pd-BOX-B (0.020 mmol), *p*-TsOH (0.30 mmol), acetonitrile (10 mL), phenylacetylene (2.0 mmol), alcohol (8.0 mmol), CO (100 psi), 110 °C, 1 h.
[b]Determined by GC based on phenylacetylene.

3.2.4. Effect of the type of alcohol

We have extended the scope of our study by considering various linear and branched alcohols as nucleophiles in the alkoxycarbonylation of phenylacetylene (Table 4, entries 1–7). The activity and selectivity were not affected by the length of the carbon chain or the presence of branching in the alcohol nucleophile. All the reactions gave high selectivity towards the formation of the *gem*-*α*,*β*-unsaturated esters **3aa**-**ag** (equation 4).



(4)

3.2.5. Effect of the type of alkyne

We have further evaluated the new catalytic system in the alkoxycarbonylation of electronically different alkynes. The palladium-*bis*(oxazoline)-phosphine complexes were active in the alkoxycarbonylation reactions of various alkynes. For instance, the methoxycarbonylation of 4-ethynylanisole (**1b**) and 4-ethynyltoluene (**1c**) were achieved to give excellent conversions and very high selectivity in the expected

Table 5. Palladium-catalyzed methoxycarbonylation of various alkynes.[a]

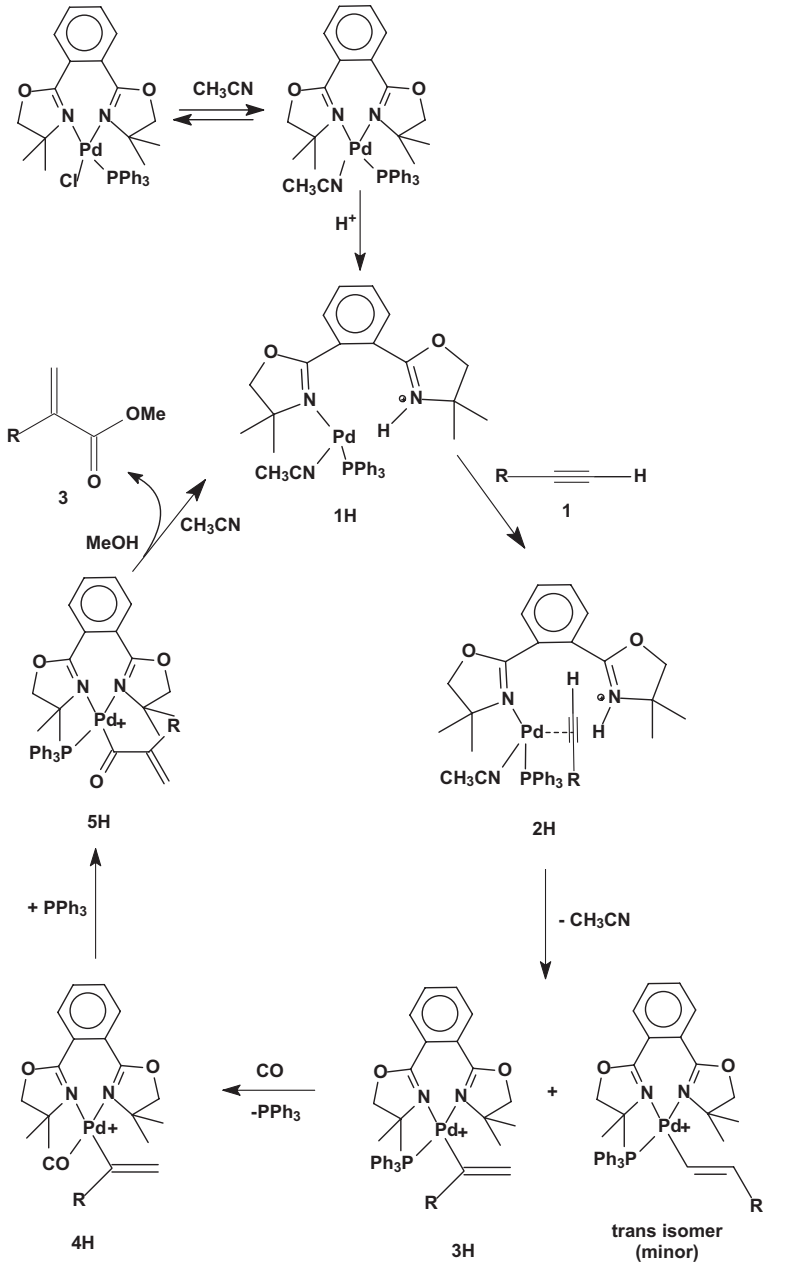
			Product distribution[b] (%)	
Entry	Alkyne	Conversion[b] (%)	**3aa-ea**	**4aa-ea**
1	Phenylacetylene	99	97	3
	1a		**3aa**	**4aa**
2	4-Ethynyltoluene	98	98	2
	1b		**3ba**	**4ba**
3	4-Ethynylanisole	99	94	6
	1c		**3ca**	**4ca**
4[c]	4-Ethynylbenzaldehyde	79	95	5
	1d		**3da**	**4da**
5[c]	1-Decyne	76	98	2
	1e		**3ea**	**4ea**

[a]Reaction conditions: Pd-BOX-B (0.020 mmol), *p*-TsOH (0.3 mmol), acetonitrile (10 mL), alkyne (2.0 mmol), methanol (8.0 mmol), CO (100 psi), 110 °C, 1 h.
[b]Determined by GC based on alkyne.
[c]6 h.

gem α,β-unsaturated esters **3ba** and **3ca** (Table 5, entries 2 and 3). Similarly, the methoxycarbonylation of the deactivated aryl alkyne (4-ethynylbenzaldehyde) (**1d**) and of the alkyl alkyne (1-decyne) (**1e**) were also achieved with high conversions and selectivities (Table 5, entries 4 and 5). Owing to the lower reactivity of these unactivated alkynes, a longer reaction time was required to achieve high conversions.

3.3. Proposed mechanism of the catalytic cycle

Two reaction pathways have been proposed for palladium-catalyzed alkoxycarbonylation of alkynes: one is based on a palladium-hydride active species (hydride cycle) [8, 28] and the other one is initiated by a palladium-alkoxy active species (alkoxy cycle) [29]. The above two mechanisms were reported to be the operating mechanisms for a variety of alkoxycarbonylation reactions of different unsaturated substrates [30–32]. The formation of palladium-hydride species is commonly proposed in the presence of acid additives [8]. However, based on the results of the screening of different reaction parameters reported above, we propose a mechanism for our catalyst systems (scheme 2). The reaction is probably initiated by the N-protonated palladium(0) *bis*(oxazoline) phosphine acetonitrile active intermediate (**1H**). This intermediate is produced via reaction of Pd-BOX-B/C with *p*-TsOH in acetonitrile. The role of acid as a protonating agent for nitrogen ligands has been proposed [33]. The proposition for protonation to occur on nitrogen rather than the phosphorus in our catalyst system is more plausible due to the higher reported basicity of amines compared to phosphines in acetonitrile [34]. The N-protonation approach is more appealing to us since the experimental results in Table 3 supported the requirement of the presence of phosphine ligand in the highly active palladium precursors in the alkoxycarbonylation of terminal alkynes. Having a coordinated solvent attached to palladium in the active intermediate (**1H**) is also expected due to the availability of solvent for this coordination. The proposed coordinating ligands will minimize the possibility of having a palladium-hydride bond in **1H** due to both steric and electronic constraints. It is also expected that the protonation step that should lead to conversion of the bidentate *bis*(oxazoline) ligand in **1H** into a monodentate mode. The bidentate palladium *cis*-dinitrogen complexes are regenerated later in the catalytic cycle [35, 36]. The next step involves direct proton transfer from the protonated *bis*(oxazoline) to the coordinated alkyne as depicted in intermediate **2H** [33]. In fact, this step will be feasible if the nitrogen of the oxazoline ring points toward the carbon of the methylene group of the coordinated alkyne, hence it can also explain the high regioselectivity obtained with our catalyst system. A full computational study on the nature of the active species and the energy barrier of proton transfer step is in progress and will be published at a later date. The resultant palladium(II) regioselective intermediate (**3H**) is subjected to (i) CO addition and insertion and (ii) methanolysis of the Pd-acyl species. The catalytic activity is independent of the type of alcohol employed as reaction nucleophile (Table 4). This rules out the methanolysis reaction path as a termination reaction [29].



Scheme 2. Alkoxycarbonylation of phenylacetylene by palladium *bis*(oxazoline) chloro phosphine complexes.

4. Conclusion

We have described the synthesis and characterization of two new palladium *bis*(oxazoline) phosphine mixed ligand complexes. The molecular structures of the new complexes were proposed based on ^{1}H, ^{13}C and ^{31}P NMR, FTIR, and ESI-MS data. We have also studied the activity and selectivity of the newly synthesized mixed ligand complexes as catalysts in the alkoxycarbonylation of alkynes. The new catalytic system showed high catalytic activity and excellent selectivity (>97%) towards the *gem*-*α*,*β*-unsaturated ester isomer under mild reaction conditions and low CO pressure. Finally, a catalytic cycle based on a

N-protonated palladium(0) *bis*(oxazoline) phosphine acetonitrile active species was proposed for our alkoxycarbonylation catalyst system. This species protonates the alkyne to produce the two palladium-vinyl key regioselective intermediates, which are subjected to further sequence of reactions that include the CO addition and insertion, alcoholysis, and reductive elimination of products.

Disclosure statement

No potential conflict of interest was reported by the authors.

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