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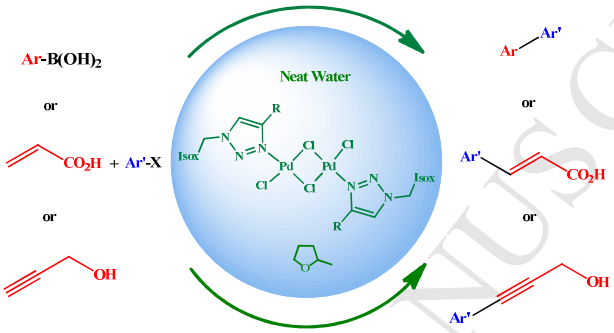

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Substituted 1-(isoxazol-3-yl)methyl-1*H*-1,2,3-triazoles: synthesis, palladium(II) complexes, and high-turnover catalysis in aqueous media

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ABSTRACT

New substituted 3-((1H-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles (aryl = Ph, p-Tol) and 2-(5-phenylisoxazol-3-yl)-5-(2-(1-((5-(p-tolyl)isoxazol-3-yl)methyl)-1H-1,2,3-triazol-4-yl)ethyl)-1,3,4-oxadiazole were synthesized by means of click-chemistry procedures. The obtained compounds were used as ligands in preparation of palladium(II) complexes, and the latter proved to be high-turnover-number catalysts for C–C cross-coupling reactions under Green Chemistry conditions. One of the ligands was structurally characterized by single crystal X-ray diffraction, and the structure of complexes was determined by ^{1}H, ^{13}C, ^{15}N NMR spectroscopy and quantum-chemical modeling.

1. Introduction

The isoxazole and 1,2,3-triazole chemistry arouse considerable interest in recent years primarily due to the unique diversity of their biological and pharmacological properties. Isoxazole and 1,2,3-triazole heterocycles are structural fragments of a large number of the bioactive molecules used in medicine as anti-cancer, antiviral, antibacterial, anti-inflammatory, anti-tubercular agents, etc.[1] It has been found over the last decades that both isoxazoles and triazoles can be successfully used as ligands for the synthesis of palladium complexes, demonstrating high catalytic activity in cross-coupling reactions.[2] The structure and functional surrounding of the heterocycle in ligand molecule significantly affect its complexation, as well as the stability and catalytic activity of the complex.

During our previous investigations, we have synthesized the air and moisture stable square-planar *trans*-dichloropalladium(II) complex, containing a 5-(*p*-tolyl)isoxazol-3-amine ligand, which proved to be a high-turnover-number catalyst for Suzuki-Miyaura reaction with a low Pd loading (0.0001–0.1 %) in neat water under air atmosphere.[3] It is reasonable to assume that the combination of the isoxazole and triazole heterocycles in the ligand structure can increase the catalytic activity of palladium complexes. Indeed, the triazole moiety contains effective coordination N-centers and readily forms complexes with transition metals.[2b] Moreover, the isoxazole and triazole rings differ in their electronic structure and donating capability, which will allow stabilizing both the Pd(0) and Pd(+2) species formed during the catalytic cycle in cross-coupling reaction. Recently, we have synthesized 5-(*p*-tolyl)isoxazol-3-(3-methyl-1*H*-1,2,4-triazol-5-yl)isoxazole ligand and its complex with $PdCl_2$, and have shown that catalytic activity of the latter is similar to that of the aminoisoxazole complex in Suzuki-Miyaura reaction in aqueous media under air but with Pd loading as low as 0.1 %.[4]

In continuation of our studies of catalysts for cross-coupling reactions[5] and development of methods for the 1,2-azole synthesis,[6] in the present work we report the synthesis of isoxazole-1,2,3-triazole ligands with a methylene bridge between the heterocycles. The basicity values of the 1,2,3- and 1,2,4-triazoles (pK_B 1.17 and 2.19, respectively) differ by

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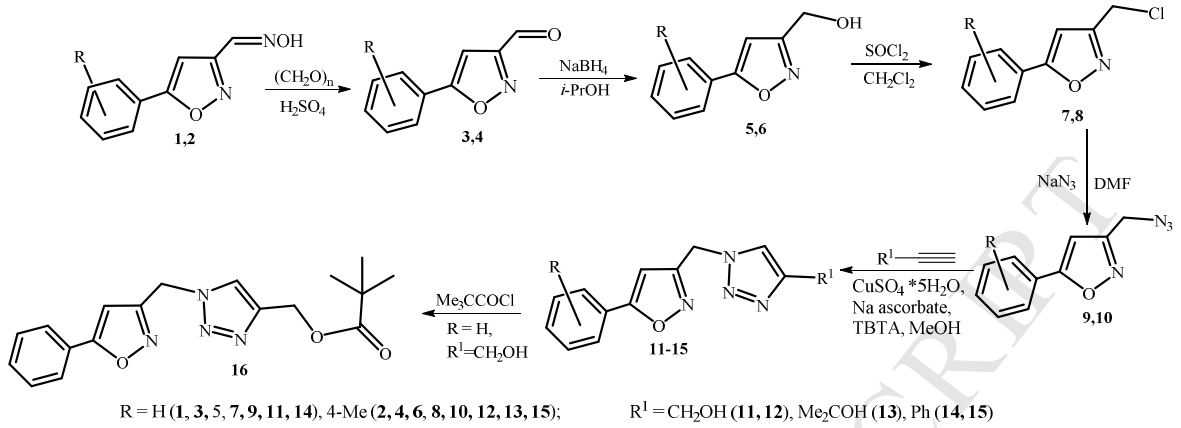
almost an order of magnitude, which certainly affects the stabilization of the complexes.[7] Furthermore, the flexibility of the nitrogen coordination of 1,2,3-triazoles provides additional opportunities in palladium catalysis.[2b] In addition, the methylene bridge between the heterocyclic fragments gives the ligand similarity to the well-studied 1-(2-picolyl)-1*H*-1,2,3-



Scheme 1. Preparation of 3-((1*H*-1,2,3-triazol-1-yl)methyl)-5-arylisoxazole derivatives **11**–**16**.

triazole ligand, which forms stable complexes with transition metals (Pd, Pt, Cu, etc.).[8] With this background in mind, we prepared new substituted 3-((1*H*-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles **11**–**16** (Scheme 1) (aryl = Ph, *p*-Tol) and 2-(5-phenylisoxazol-3-yl)-5-(2-(1-((5-(*p*-tolyl)isoxazol-3-yl)methyl) -1*H*-1,2,3-triazol-4-yl)ethyl)-1,3,4-oxadiazole **20** (Scheme 2).

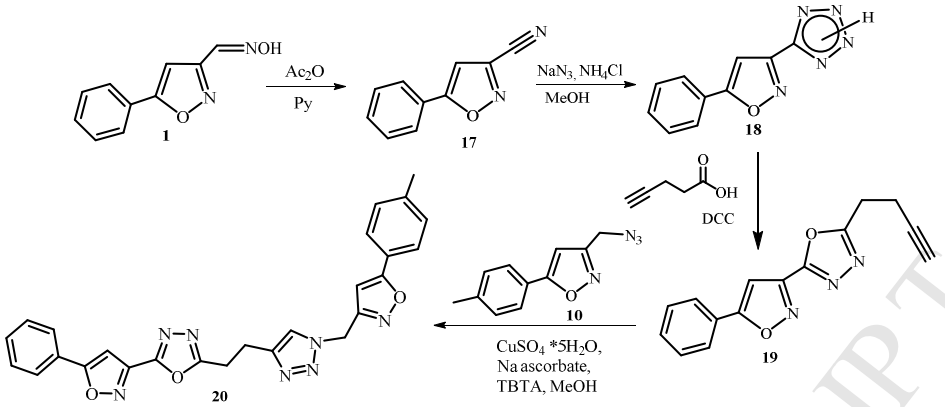
These ligands were reacted with Na_2PdCl_4 to give the palladium(II) complexes L^1PdCl_2–L^7PdCl_2. Herein, we present the detailed synthesis of the ligands and palladium(II) complexes together with their characterization and catalytic activity testing as new catalysts for C–C cross-coupling reactions in neat water under ambient atmosphere. It is also important to note that 3-((*1H*-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles are of special interest for biological testing in different domains, for example, as anti-cancer agents and isosteres of 3-(aryl-1*H*-1,2,3-triazol-1-yl)benzisoxazole that exhibit high anticancer activity in acute myeloid leukemia cell lines.[1b,9]

2. Results and Discussion

2.1. Design and synthesis of ligands

Our synthetic strategy for the preparation of desired 3-((*1H*-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles **11**–**16** and bis-isoxazole-1,2,3-triazole-1,3,4-oxadiazole ligand **20** involved the formation of the (1*H*-1,2,3-triazol-1-yl)methyl molecular fragment in position 3 of the 5-arylisoxazoles by Cu(I) catalyzed 1,3-dipolar cycloaddition (click reaction)[10] of the isoxazole azides with respective acetylene derivatives (Scheme 1). As azide components we chose 3-(azidomethyl)-5-arylisoxazoles **9,10** which were synthesized by the action of NaN_3 on the 3-(chloromethyl)-5-arylisoxazoles **7,8**. The synthesis of azidomethylisoxazoles **9,10** was carried out in DMF solution at 40 °C giving the products in quantitative yield. Starting 5-arylisoxazoles **7,8** were obtained via successive transformation of available 5-arylisoxazole-3-carbaldehyde oximes **1,2** into corresponding 5-arylisoxazole-3-carbaldehydes **3,4** and then 5-arylisoxazol-3-yl methanols **5,6**.[6b,11] The obtained azidomethylisoxazoles **9,10** were introduced in the reaction of 1,3-dipolar cycloaddition with different alkynes (propargyl alcohol, 2-methylbut-3-yn-2-ol, phenylacetylene) under classic conditions of the click-chemistry ($CuSO_4 \cdot 5H_2O$, sodium ascorbate, TBTA – tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine, MeOH) and it resulted in isolation of corresponding 3-((*1H*-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles **11-15** in high yields (91–99 %). Acylation of (1-((5-phenylisoxazol-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methanol **11** with pivaloyl chloride, afforded (1-((5-phenylisoxazol-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl pivalate **16**, which turned out to be useful for further NMR studies of the Pd(II) complexes structure.

The 3-(azidomethyl)-5-(*p*-tolyl)isoxazole **10** was also applied in the synthesis of the polycyclic derivative - 3-((*1H*-1,2,3-triazol-1-yl)methyl)-5-arylisoxazole with several azole heterocycles in one molecule **7**. As alkyne co-reagent in the click reaction with azidomethylisoxazole **10**, 2-(but-3-yn-1-yl)-5-(5-phenylisoxazol-3-yl)-1,3,4-oxadiazole **19** was used which was synthesized from the previously described 3-(1*H*-tetrazol-5-yl)-5-phenylisoxazole **18**.[4] The tetrazole part of isoxazolyltetrazole molecule **18** was transformed into butynyl-1,3,4-oxadiazolic molecular fragment by selective recyclisation of tetrazole heterocycle (Scheme 2).[12] This was accomplished



Scheme 2. Preparation of bis-isoxazole-1,2,3-triazole-1,3,4-oxadiazole **20**.

by treating isoxazolyltetrazole **18** with pent-4-ynoic acid in the presence of DCC (N,N'-dicyclohexylcarbodiimide). The process involved tetrazole acylation and elimination of nitrogen to form 2-butynyl-5-(5-phenylisoxazoyl)-1,3,4-oxadiazole **19** in 86 % yield. The structures of synthesized isoxazolyl-1,2,3-triazoles **11-16**, bis-isoxazolyl-1,2,3-triazole-1,3,4-oxadiazole **20**, azidomethylisoxazoles **9,10** and isoxazolyl-1,3,4-oxadiazole **19** were confirmed by IR, ^{1}H and ^{13}C NMR spectra as well as by single crystal X-ray analysis of (1-((5-phenylisoxazol-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methanol **1**. The obtained isoxazole-1,2,3-triazoles **11**–**16** and bis-isoxazole-1,2,3-triazole-1,3,4-oxadiazole **20** were used then as ligands (L^1–L^7) in the synthesis of Pd(II) complexes L^1PdCl_2–L^7PdCl_2, aiming evaluation of the latter catalytic activity in cross-coupling reactions. They were synthesized by reaction of ligands with Na_2PdCl_4 in methanol solutions. Addition of 0.025 M solution of ligand (**11**–**16, 20**) in MeOH to a 0.1 M solution of sodium tetrachloropalladate in methanol induced a quick disappearance of a characteristic dark brown color of Na_2PdCl_4 and formation of the complex precipitate. Complete consumption of the starting ligands in the reaction mixture was observed within 5 min.

The obtained palladium(II) complexes were identified by elemental analysis and IR spectroscopy. According to elemental analysis data, all complexes are of general formula $LPdCl_2$. Because the synthesized complexes were amorphous powders with low solubility in organic solvents, we were not able to perform their X-ray analysis and faced problems with registration of NMR data and mass-spectra. Therefore, the structure determination of complexes was based on the analysis of 2D NMR (^{1}H, ^{13}C, ^{15}N) and mass-spectra of the most soluble complexes L^1PdCl_2 (L^1 = (1-((5-phenylisoxazol-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methanol **11**) and L^6PdCl_2 (L^6 = (1-((5-phenylisoxazol-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl pivalate **16**) as well as on the results of quantum-chemical calculations of molecular geometry and vibrational frequencies for L^1PdCl_2 followed by comparison of the calculated values of frequencies with the experimental IR spectrum.

*2.2. Crystal structure of compound **11***

Single crystals of compound **11** suitable for X-ray analysis were obtained by slow evaporation of acetone–chloroform (1:1 v/v) solution (Figure 1).

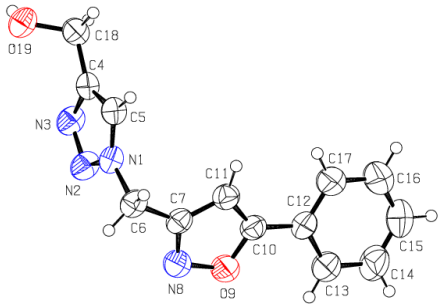


Figure 1. Molecular structure of **11,** with the atom-numbering scheme and displacement ellipsoids drawn at the 50 % probability level. The hydrogen atoms are shown as spheres of arbitrary radii. Bond lengths in heterorings: N1–N2 = 1.3345(16), N1–C5 = 1.3383(18), N2–N3 = 1.3138(17), N3–C4 = 1.3559(18), C4–C5 = 1.3639(19) Å; C7–N8 = 1.300(2), C7–C11 = 1.405(2), N8–O9 = 1.4104(17), O9–C10 = 1.3512(18), C10–C11 = 1.342(2) Å.

Crystal data and structure refinement details for the compound are gathered in Table 1. As follows from X-ray analysis of compound **11,** it crystallizes in the triclinic space group $P\bar{1}$ with two formula units in the unit cell and one molecule in the asymmetric unit (Figure 2).

Table 1. Single crystal X-ray data and structure refinement details for **11**.

Formula	$C_{13}H_{12}N_4O_2$
Formula weight	256.27
Temperature [K]	296(2)
Wavelength [Å]	0.71073
Crystal system	Triclinic
Space group	P
a [Å]	5.90940(10)
b [Å]	7.81760(10)
c [Å]	14.5953(3)
α [°]	100.2381(9)
β [°]	94.2600(11)
γ [°]	110.7872(11)
V [Å^3]	613.382(19)

Z	2
d_{calcd} [g cm^{-3}]	1.388
μ [mm^{-1}]	0.098
Crystal size [mm]	0.38 × 0.20 × 0.18
Reflections collected	5770
Independent reflections	5770 [R(int) = 0.0186]
Restraints	0
Parameters	174
Goodness-of-fit	1.020
R1 / wR2 [I > 2σ(I)]	0.0429 / 0.1063
R1 / wR2 [all data]	0687 / 0.1213
CCDC	1823325

Bond lengths and valence angles in heterocycles show usual values. There are intermolecular hydrogen bonds in the crystal structure of **11** (Table 2). Classic hydrogen bonds O19–H19···N3^a between the hydroxyl H and the 1,2,3-triazole ring N atoms of neighboring molecules form centrosymmetric dimers, linked together by non-classic hydrogen bonds C18-H18A···N2^b to give polymeric ribbons running along the *a* axis (Figure 2) [symmetry codes (a) and (b) as in Table 2]. Only van der Waals interactions take place between the ribbons.

Table 2. Hydrogen bonds geometry (Å, deg) in the crystal structure of **11**.

D–H···A	D–H	D···A	D–H···A)
O19-H19...N3^a	0.82	2.8308(16)	170
C18-H18A...N2^b	0.97	3.449(2)	164

Symmetry codes: (a) –x, 1–y, 1–z; (b) x+1, y, z.

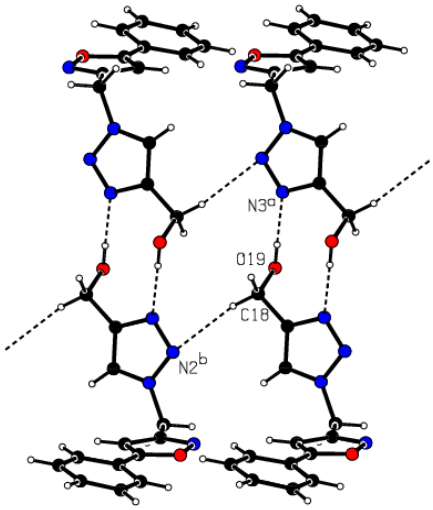


Figure 2. Fragment of hydrogen-bonded ribbon in the crystal structure of **11**. Symmetry codes (a) and (b) as in Table 2.

2.3. NMR spectra of complexes L^1PdCl_2 and L^6PdCl_2

Along with X-ray analysis, NMR methods are powerful tools for structure elucidation of organic complexes. We have carried out a comparative study of two palladium(II) complexes and their ligands by the correlation NMR spectroscopy methods in order to estimate the most probable position of Pd and the ligand coordination. As follows from a comparison of the ^{1}H and ^{13}C NMR spectra of ligands L^1, L^6 and corresponding complexes L^1PdCl_2 and L^6PdCl_2, the most significant changes in the chemical shifts are observed for the triazole part of molecules (2–3 ppm downfield in the ^{13}C spectra and 0.2–0.3 ppm downfield in the ^{1}H spectra). Values of the chemical shifts of the isoxazole residue signals change twice as less. This allowed us to assume that the Pd is coordinated with the triazole molecular fragment. Due to a low abundance of ^{15}N, the chemical shifts of ^{15}N nuclei were determined by the use of the ^{1}H-^{15}N-HMBC method (see Figure 3).

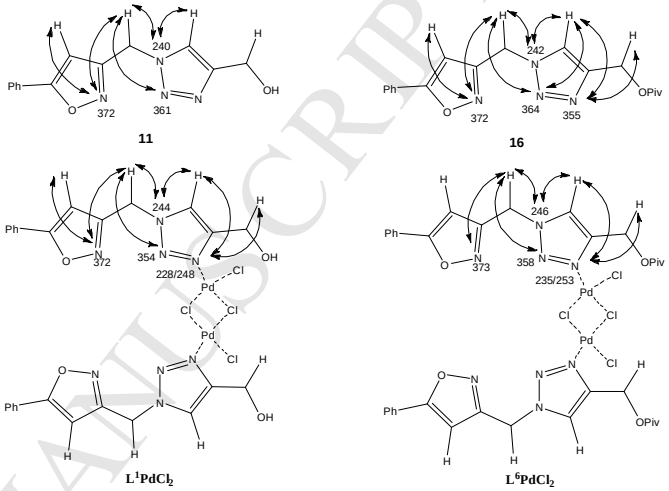
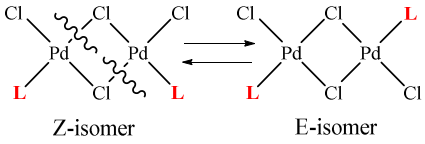


Figure 3. ^{15}N chemical shifts and the observed ^{15}N-^{1}H interactions in the HMBC spectra of compounds **11**, **16**, L^1PdCl_2, L^6PdCl_2.

Such method allowed assigning three nitrogen nuclei of ligand L^1: N^1 (cross-peaks with 5-H and CH_2-group), N^2 (cross-peak with 5-H) of the triazole ring and $N^{2'}$ of isoxazole ring (cross-peaks with 4'-H and CH_2-group). The signal of N^3 atom of the triazole ring was not found (expected cross-peak with $HOCH_2$-group[13,14]) despite the execution of several NMR experiments by varying of the ^{1}H-^{15}N coupling constant (1–8 Hz). This result caused the exact coordination of Pd determination in the complex less reliable. One of the reasons for the observed effect may be an influence of the H-bonds OH···N^3 of neighboring molecules, as it was established by X-ray analysis (see Figure 2). To exclude the effect of H-bonds, we acylated the OH group of ligand L^1 with pivaloyl chloride to prepare ester **16** (ligand L^6) as was described above. Indeed, in the ^{1}H-^{15}N-HMBC spectrum of pivalate **16** we observed the signals of all four nitrogen atoms (N^3 had a cross-peak with the CH_2OPiv group and resonated at 355 ppm). Comparison of the spectra of the ligand L^6 and the complex L^6PdCl_2 unambiguously indicates the coordination of Pd with the atom N^3. While the signals of the rest complex nitrogens resonated closely to those of ligand L^6, the signal of N^3 was found almost 100 ppm upfield. The similar pattern of the ^{1}H-^{15}N-HMBC spectrum was registered also for the complex L^1PdCl_2. Such significant shielding influence on the nitrogen nuclei coordinated with Pd was already shown for triazoles and other nitrogen heterocycles.[15, 16] It should be noted that series of the signals in ^{1}H, ^{13}C and ^{15}N NMR spectra appear as couples with a close intensity. This may be due to the existence of complexes in the form of bridge structures, with the possibility of rotation around Pd–N^3 bond and the formation of rotamer couples. Another reason may be the existence of a complex as a mixture of *E,Z*-isomers in the bridge fragment of the molecule. The ratio of rotamers, as well as the ratio of isomers, should depend on the

temperature. We recorded the ^{1}H, ^{13}C and ^{1}H-^{15}N-HMBC NMR spectra for the $L^{6}PdCl_2$ complex at 65 °C and found that the signals ratio changed substantially and one of the rotamers (or isomers) became predominant. It should be noted that after cooling to room temperature, the signal ratio remains the same as at 65 °C. This might indicate realization of the isomerization process (Scheme 3). The correlation spectra give opportunity to determinate proton/carbon signals of each rotamers (isomers) in the triazole part of the complex molecules. Thus, the complexes with the downfield N^3 NMR signal (248 ppm - $L^{1}PdCl_2$ and 253 ppm - $L^{6}PdCl_2$) have downfield proton signals (5.33 and 5.78 ppm – CH_2O, 8.50 and 8.73 ppm - $H_{triazol}$ for $L^{1}PdCl_2$ and $L^{6}PdCl_2$ respectively). The resonances of the carbon nuclei depend on the position of these nuclei in the molecule. For example, the signals of CH_2-group and $C_{triazol}$ carbons are upfield (47.32, 57.69 and 145.12 ppm) whereas the $CH_{triazol}$ signal is observed in downfield (128.17 ppm) of the $L^{6}PdCl_2$ isomer with 253 ppm of the N^3 NMR signal.



Scheme 3. Principal scheme of dimeric complex isomerization.

2.4. Mass-spectometry of complexes $L^{1}PdCl_2$ and $L^{6}PdCl_2$

Our numerous attempts to perform a mass-spectrometric study of the complexes were unsuccessful. The problem lays not only in a low solubility of the complexes compounds, but it is connected with their stability in the ESI-MS-experiment as well as nature of the ligands. Nevertheless, we were able to observe fragment ions of low intensity ($[M - Cl^-]^+$ for dimers) in the case of the most soluble complexes $[L^{1}PdCl_2]_2$ and $[L^{6}PdCl_2]_2$ (Figure 1, SI). As shown in Figure 1 (SI), the fragment ions $[M – Cl^-]^+$ at *m*/z 826-839 (830.942) for $[L^{1}PdCl_2]_2$ and 994-1006 (998.988) for $[L^{6}PdCl_2]_2$ were detected. Moreover, peaks due to species containing Pd were easily detected by the characteristic isotope distribution of the metal [$^{101.9}$Pd (1%), $^{103.9}$Pd (11.1%), $^{104.9}$Pd (22.3%), $^{105.9}$Pd (27.3%), $^{107.9}$Pd (26.5%) and $^{109.9}$Pd (11.7%)]. Theoretical isotope patterns were calculated by MestReNova program and used to help the assignment (file mass-spectra, SI).

2.5. Quantum-chemical modeling of $L^{1}PdCl_2$ complex

Additionally, we compared experimental IR spectra of synthesized complex $L^{1}PdCl_2$ with modeled vibrational spectra for the complex of dimeric structure. Full geometry optimization of the latter and its normal-mode vibrational frequencies calculations were carried out at DFT level of theory, using B3LYP1[17] functional in combination with Pople's 6-31+G* basis set[18,19] for main-groups elements, and LANL2TZ(f) basis set with corresponding effective core potential[20] for palladium. All basis sets were obtained through EMSL Basis Set Exchange Library.[21] The applicability of this level of theory for modeling of some 1,2-azoles palladium complexes structures and their normal-mode vibrational frequencies calculation was shown previously,[6b] as well as the application of scale factors for analysis of obtained frequencies.[22] In the present work, we used a scale factor of 0.978. For calculations we used Firefly QC package.[23] which is partially based on the GAMESS (US)[24] source code. The results of the calculations were analyzed with the help of ChemCraft package.[25] Experimental frequencies for complex $L^{1}PdCl_2$ and calculated vibrational frequencies are listed in Table 3, obtained geometry for the dimeric complex is presented in Figure 3.

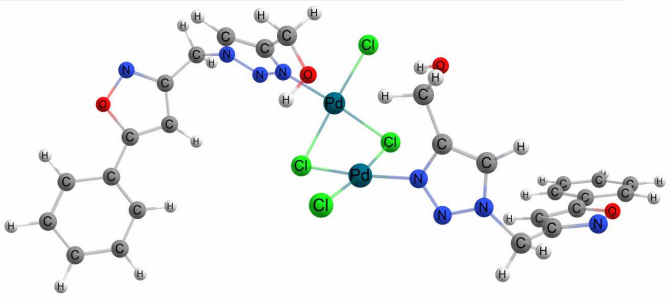


Figure 4. The optimized geometry of dimeric complex $L^{1}PdCl_2$.

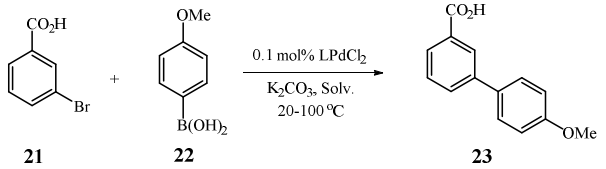
Calculated vibrational frequencies appeared to be in good agreement with experimental IR spectra of synthesized compound $L^{1}PdCl_2$. Therefore, these data support the hypothesis about a dimeric structure of the complex with coordination of palladium atom by the triazole ring N^3 atom. It should be noted that we also modeled structural parameters for ligand L^1 on the same level of theory. The difference between calculated geometrical parameters and parameters obtained through single crystal X-Ray diffraction for substance **11** (L^1) did not exceed 0.03Å for bond lengths and 3 degrees for angles. The only significant difference that was observed is the conformational position of isoxazole ring relatively to the triazole fragment.

Table 3. Main experimental IR spectra bands and calculated vibrational frequencies for complex $L^{1}PdCl_2$.

Oscillation type (highest contribution)	Experimental frequencies, cm^{-1}	Calculated frequencies, cm^{-1}
$\delta(C\text{-}C)_{arom}$	492	494
$\delta(C\text{-}C, C\text{-}H)_{arom} + \delta(C\text{-}H)_{isox}$	688	686
$\delta(C\text{-}C, C\text{-}H)_{arom} + \delta(C\text{-}H)_{isox} + \delta(C\text{-}H)_{triaz}$	764	765
$\delta(C\text{-}H)_{isox} + \delta(C\text{-}H)_{triaz} + \delta(CH_2)$	797	786
$\delta(CH_2) + \delta(C\text{-}CH\text{-}C)_{isox} + \delta(O\text{-}H)$	950	952
$\nu(C\text{-}O)_{OH}$	1024	1027
$\nu(C\text{-}O)_{OH} + \delta(N\text{-}N\text{-}N)_{triaz} + \delta(C\text{-}CH\text{-}N)_{triaz}$	1050	1047
$\delta(C\text{-}H)_{isox} + \nu(C\text{-}O)_{isox} + \nu(C\text{-}H)_{arom}$	1062	1054
$\delta(C\text{-}H)_{triaz} + \delta(N\text{-}N_{Pd}\text{-}C)_{triaz} + \nu(C\text{-}C)_{triaz}$	1095	1093
$\delta(C\text{-}H)_{triaz} + \delta(N\text{-}N\text{-}CH)_{triaz} + \delta(CH_2)$	1147	1146
$\delta(C\text{-}H)_{arom} + \nu(O\text{-}C)_{isox} + \nu(C_{isox}\text{-}C_{arom})$	1250	1256
$\nu(N_{Pd}\text{-}N)_{triaz} + \delta(CH_2) + \delta(O\text{-}H)$	1259	1272
$\delta(CH_2)$	1340	1354
$\delta(CH_2) + \nu(CH\text{-}N)_{triaz}$	1420	1444
$\delta(C\text{-}H)_{arom} + \delta(C\text{-}H)_{isox} + \nu(C\text{-}CH)_{isox}$	1455	1463
$\delta(C\text{-}H)_{arom} + \nu(C\text{-}N)_{isox} + \nu(C\text{-}CH)_{isox}$	1474	1475
$\nu(C\text{-}N)_{isox} + \nu(C\text{-}C)_{arom} + \delta(C\text{-}H)_{arom}$	1504	1512
$\delta(C\text{-}H)_{triaz} + \nu(C\text{-}C)_{triaz}$	1573	1561
$\delta(C\text{-}H)_{arom} + \nu(C\text{-}C)_{isox} + \nu(C\text{-}C)_{arom}$	1591	1584
$\delta(C\text{-}H)_{arom} + \nu(C\text{-}C)_{arom} + \nu(C\text{-}C)_{isox}$	1609	1603

2.6. Complexes in catalysis of cross-coupling reactions

With synthesized water and air-stable complexes L^1PdCl_2 – L^7PdCl_2 in hand, we further tested their catalytic activity in cross-coupling reactions. Primarily, to test the activity of $LPdCl_2$ for the Suzuki-Miyaura reactions, the model reaction of 3-bromobenzoic acid **21** with 4-methoxyphenylboronic acid **22** in the presence of 0.1 mol % of $LPdCl_2$ was studied under air atmosphere (Scheme 4, Table 4). Water and aqueous methanol were used as solvents and K_2CO_3 as a base for these reactions, based on our previous results.[3,5l]



21 **22** **23**

Scheme 4. Model Suzuki-Miyaura reaction: cross-coupling of 3-bromobenzoic acid **21** with 4-methoxyphenylboronic acid **22** (0.1 mol % of $LPdCl_2$) yielding 4-methoxybiphenyl-3-carboxylic acid **23**.

Table 4. Suzuki-Miyaura reaction of 3-bromobenzoic acid **21** with 4-methoxyphenylboronic acid **22** in the presence of complexes $LPdCl_2$[a].

Entry	$LPdCl_2$	T[b], °C	Time, min	Yield,[c] % TON/TOF, h^{-1}
1	L^1PdCl_2	20	15	99 $9.9\cdot10^2/3.96\cdot10^3$
2	L^1PdCl_2	100	2	100 $1\cdot10^3/3\cdot10^4$
3	L^2PdCl_2	20	15	100 $1\cdot10^3/4\cdot10^3$
4	L^2PdCl_2	75	2	100 $1\cdot10^3/3\cdot10^4$
5	L^2PdCl_2	35	10	100 $1\cdot10^3/6\cdot10^3$
6	L^2PdCl_2	100	2	100 $1\cdot10^3/3\cdot10^4$
7	L^2PdCl_2 0.01 mol %	100	4	100 $1\cdot10^4/1.5\cdot10^5$
8	L^2PdCl_2 0.001 mol %	100	5	100 $1\cdot10^5/1.2\cdot10^6$
9[d]	L^2PdCl_2 0.0001 mol %	100	5	100 $1\cdot10^6/1.2\cdot10^7$
10	L^3PdCl_2	20	15	98 $9.8\cdot10^2/3.92\cdot10^3$
11	L^3PdCl_2	100	2	99 $9.9\cdot10^2/2.97\cdot10^4$
12	L^4PdCl_2	20	20	98 $9.8\cdot10^2/2.94\cdot10^3$
13	L^4PdCl_2	100	<1	100 $1\cdot10^3/6\cdot10^4$
14	L^5PdCl_2	35	15	100 $1\cdot10^3/4\cdot10^3$
15	L^5PdCl_2	75	<1	99 $9.9\cdot10^2/5.94\cdot10^4$
16	L^6PdCl_2	20	15	100 $1\cdot10^3/4\cdot10^3$
17	L^6PdCl_2	100	<1	98 $9.8\cdot10^2/5.88\cdot10^4$
18	L^7PdCl_2	20	20	97 $9.7\cdot10^2/2.91\cdot10^3$
19	L^7PdCl_2	100	3	100 $1\cdot10^3/2\cdot10^4$
20	Na_2PdCl_4	20	10 4 h	89 92
21	Na_2PdCl_4	100	5	99 $9.9\cdot10^2/1.19\cdot10^4$

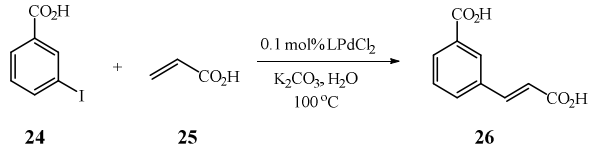
[a] Aryl halide (0.5 mmol), arylboronic acid (0.6 mmol), K_2CO_3 (1.25 mmol), 5 ml of solvent: H_2O or H_2O-MeOH (1:1).
[b] The experiments were performed in aqueous methanol solution at 20 and 75 °C or in water at 35 and 100 °C.
[c] ^1H NMR yield with 1,1,2,2-tetrachloroethane (0.5 mmol) as internal standard.
[d] Reaction with 3-iodobenzoic acid.

It should be noted that in the presence of the base, 3-bromobenzoic acid was converted into the corresponding soluble potassium benzoate and the reaction proceeded under homogeneous conditions. We found that the reaction proceeded smoothly at 20–35 °C in 10–15 min in a high yield without any inert gas protection in the presence of tested complexes (Table 4, entries 1, 3, 5, 10, 12, 14 and 16). At elevated temperatures (75–100 °C), the reaction time did not exceed 1–4 min (entries 2, 4, 6, 11, 13, 15, 17 and 19). Much to our surprise, in all cases the reaction proceeded without any apparent formation of Pd-black, even after the complete conversion of the aryl halide. To understand this phenomenon, we assumed that only a negligible part of the original Pd(II) complex was reduced to the active complex Pd(0) and participated in the catalytic cycle. Consequently, if this assumption is correct, the reaction can be carried out with a lower catalyst loading. Indeed, the amount of catalyst can be reduced by an order of magnitude or more, without appreciable decrease in activity. For example, in the presence of 0.01–0.001 mol % of complex L^2PdCl_2, 3-bromobenzoic acid reacted with 4-methoxyphenylboronic acid in water at 100 °C in 4–5 min in quantitative yields with turnover numbers (TON) up to 100,000 and turnover frequencies (TOF) up to 1,200,000 h^{-1} (entries 7 and 8). In the case of aryl iodides, the reaction was completed in less than 5 min with high yield in the presence of 0.0001 mol % of catalyst (1 ppm level). Remarkably high TON of 1,000,000 and TOF of 12,000,000 h^{-1} were achieved (entry 9). These results indicate that isoxazolyl-1,2,3-triazole complexes L^1PdCl_2–L^7PdCl_2 are very effective and high-turnover catalysts for Suzuki-Miyaura reaction in aqueous media.

On the other hand, the use of Na_2PdCl_4 as the catalyst in aqueous methanol at room temperature afforded cross-coupling product in 89 % yield in 10 min (Table 4, entry 20). However, at this moment, the catalyst agglomerated completely into Pd-black. After the formation of the Pd-black, the reaction almost stopped, and within 4 h the yield increased to only 92 % (entry 20). At elevated temperature, the cross-coupling product was formed with a quantitative yield in 5 min (entry 21).

The catalytic activity of $LPdCl_2$ complexes was not limited to Suzuki-Miyaura reactions. It can be readily extended to other cross-coupling reactions such as Mizoroki-Heck[26] and Sonogashira[27] reactions.

We evaluated catalytic activity of some $LPdCl_2$ complexes in the Mizoroki–Heck reaction between *m*-iodobenzoic acid **24** and acrylic acid **25** in the presence of K_2CO_3 under reflux in water to give 3-carboxy-*trans*-cinnamic acid **26** (Scheme 5, Table 5).



24 **25** **26**

Scheme 5. Model Mizoroki–Heck reaction: cross-coupling of *m*-iodobenzoic acid **24** and acrylic acid **25**.

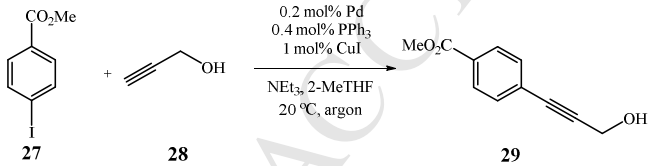
Table 5. Mizoroki–Heck reaction between m-iodobenzoic acid **24** and acrylic acid **25** in the presence of complexes $LPdCl_2$[a].

Entry	$LPdCl_2$	Time, min	Yield,[b]% TON/TOF, h^{-1}
1	L^2PdCl_2	30	99 $9.9\cdot10^2/1.98\cdot10^3$
2	L^4PdCl_2	30	100 $1\cdot10^3/2\cdot10^3$
3	L^6PdCl_2	30	100 $1\cdot10^3/2\cdot10^3$
4	L^7PdCl_2	40	98 $9.8\cdot10^2/1.96\cdot10^3$

[a] Aryl halide (0.5 mmol), acrylic acid (0.6 mmol), K_2CO_3 (1.25 mmol), 5 mL of H_2O, 100 °C.
[b] ^1H NMR yield with 1,1,2,2-tetrachloroethane (0.5 mmol) as internal standard.

For all tested complexes, almost quantitative isolated yields of **26** were obtained in 30–40 min in air atmosphere. No by-products were detected for any of the catalysts, and cinnamic acid **26** was isolated in pure form without the need of chromatographic purification.

Finally, $LPdCl_2$ complexes were assayed in the Sonogashira reaction between methyl *p*-iodobenzoate **27** and prop-2-yn-1-ol (propargyl alcohol) **28**, to afford methyl 4-(3-hydroxyprop-1-yn-1-yl)benzoate **29** (Scheme 6), under the conditions summarized in Table 5 (2-methyltetrahydrofuran, 1.5 eq. of triethylamine as base, 0.2 mol % $LPdCl_2$ + $2PPh_3$, 1 mol % CuI, 20 °C, 15 min, argon).



27 **28** **29**

Scheme 6. Model Sonogashira reaction: cross-coupling of *p*-iodobenzoate **27** and prop-2-yn-1-ol **28**.

It is important to note that it was the use of an additional phosphine ligand that provided a smooth reaction and a high yield (Table 6, entries 1, 3, 4 and 6). In the absence of triphenylphosphine, the reaction proceeded quickly but mainly resulted in the formation of tar products of an unidentified structure (entries 2 and 5). It is possible that without additives the activity of the resulting palladium catalyst is so high that it causes oligomerization [28] of the acetylene compounds, both the starting propargyl alcohol and the cross-coupling product. The practical advantage of this protocol is the use of water-insoluble 2-MeTHF as a solvent, which provides convenient isolation of cross-coupling products by separation of 2-MeTHF–water layers, then evaporation and full regeneration of 2-MeTHF. The growing interest towards 2-MeTHF from both academia and industries is also due to its abidance of Green Chemistry principles.[29]

Table 6. Sonogashira reaction between methyl p-iodobenzoate **27** and prop-2-yn-1-ol 28 in the presence of complexes $LPdCl_2$[a].

Entry	$LPdCl_2$	Additives	Time, min	Yield,[b] % TON/TOF, h^{-1}
1	L^2PdCl_2	PPh_3	15	97 $9.7\cdot10^2/3.88\cdot10^3$
2	L^2PdCl_2	–	10	23
3	L^4PdCl_2	PPh_3	15	99 $9.9\cdot10^2/3.96\cdot10^3$
4	L^6PdCl_2	PPh_3	15	98 $9.8\cdot10^2/3.92\cdot10^3$
5	L^6PdCl_2	–	10	19
6	L^7PdCl_2	PPh_3	20	96

[a] Aryl halide (0.5 mmol), prop-2-yn-1-ol (0.65 mmol), NEt_3 (0.75 mmol), 1 mol % CuI, 5 mL of 2-MeTHF, 20 °C.

[b] ^1H NMR yield with 1,1,2,2-tetrachloroethane (0.5 mmol) as internal standard.

It is worthwhile noting that $(PPh_3)_2PdCl_2$ afforded **29** in 82 % yield after a prolonged reaction time (THF, 4 eq. of triethylamine, 1.5 mol % Pd-catalyst, 1.5 mol % CuI, 20 °C, overnight, argon).[30]

3. Conclusions

An efficient and convenient synthesis of new substituted 3-((1*H*-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles (aryl = Ph, p-Tol) and 2-(5-phenylisoxazol-3-yl)-5-(2-(1-((5-(*p*-tolyl)isoxazol-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)eth-yl)-1,3,4-oxadiazole was elaborated by means of click-chemistry procedures. The new compounds served as ligands in preparation of water and air-stable palladium(II) complexes. The obtained complexes demonstrated high catalytic activity in the cross-coupling reactions: 3-bromobenzoic acid with 4-methoxyphenylboronic acid (Suzuki-Miyaura reaction), *m*-iodobenzoic acid with acrylic acid (Mizoroki–Heck reaction) and methyl *p*-iodobenzoate with propargyl alcohol (Sonogashira reaction). All reactions proceeded in short time in water or environment friendly solvent with quantitative yields of the target products. Currently, these palladium complexes are being studied as precursors for the development of effective homogeneous and reusable heterogeneous catalysts for the synthesis of useful products in environmentally safe conditions (Green Chemistry).

4. Experimental Section

4.1. General Information

The IR spectra were recorded on a FTIR spectrometer Protege-460 (Nicolet) in KBr pellets. ^1H, ^{13}C and ^{15}N NMR spectra were recorded on a Bruker Avance-500 spectrometer operating at 500, 125, and 51 MHz for ^1H, ^{13}C and, ^{15}N, respectively. Chemical shifts are given on the δ scale (ppm) and were determined relative to the residual solvent signal (δH 7.26 ppm, δC 77.2 ppm for $CDCl_3$; δH 2.5 ppm, δC 40.1 -ppm for DMSO-d_6, δH 8.0 ppm, δC 162.5 ppm for DMF-d_7). Nitrogen chemical shift values for ^{15}N NMR spectra were assigned relative to the nitromethane used as an internal reference (δN 380.0 ppm). Coupling constants (J) are given in Hertz. Assignments of proton and carbon resonances were performed by standard 2D NMR

techniques (^{1}H,^{1}H-COSY, HSQC, HMBC). Mass spectra were recorded on an instrument Agilent 5975 inert MSD/6890N Network GC System (EI ionisation at 70 eV), HP-5MS capillary column 30 m × 0.25 mm, 5% PhMe Silicon stationary phase (0.25 μm), evaporator temperature 250 °C. Data are reported as m/z (relative intensity in %). HPLC-MS studies were performed using an Agilent 1200 liquid chromatograph with mass-selective detector Agilent 6410 Triple Quad in Positive ESI mode. Elemental analysis was performed on a Vario Micro cube CHNS-analyser. The chlorine content was determined by classical microanalysis according to the modified Pregl method.[31] The palladium content of complexes and residual palladium contamination in target products was determined by atomic absorption spectroscopy on a MGA-915 spectrometer. TLC was performed on Merck Silica gel 60 F_{254} plates; the eluent was hexane–Et_2O, 2:1-1:3. Melting points were determined on Boetius apparatus. All purchased chemicals were used as such.

Single crystal X-ray diffraction data of **11** were collected on a SMART Apex II diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) at a temperature of 296 K. The structure was solved by direct methods (SIR2014[32]) and refined on F^2 by the full-matrix least-squares technique (SHELXL2016[33]). The intensities were corrected for absorption. For all compounds, non-hydrogen atoms were refined anisotropically. The investigated crystal was a non-merohedral twin, with a fractional contribution of 0.5079 (12) of the major twin component. The hydrogen atoms were placed in calculated positions and refined in a "riding" model, with U_{iso}(H) = 1.5U_{eq}(O) for the hydroxyl H atom and U_{iso}(H) = 1.2U_{eq}(C) for remaining H atoms. Molecular graphics was performed with the programs ORTEP-3 for Windows[34] and PLATON.[35]

4.2. General Procedure for the Synthesis of 3-(Azidomethyl)-5-arylisoxazoles ***(9,10)***

Sodium azide (11 mmol) was added to the corresponding 3-(chloromethyl)-5-arylisoxazole **7,8** (10 mmol) in 20 mL anhydrous DMF and the mixture was stirred for 4 h at 65–70 °C. The reaction mixture was then poured into ice water saturated with NaCl. The precipitate was filtered off, washed with water (3 x 20 mL) and dried over P_2O_5.

4.3. 3-(Azidomethyl)-5-phenylisoxazole ***(9)***

White solid (99 % yield); m.p. 45–46 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.45 (s, 2H, CH_2), 7.23–7.19 (m, 1H), 6.65 (s, 1$H_{isox.}$), 7.38–7.51 (m, 3$H_{arom.}$), 7.70–7.82 (m, 2$H_{arom.}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.82 (CH_2), 98.59 ($CH_{isox.}$), 125.93 (2$CH_{arom.}$), 129.11 (2$CH_{arom.}$), 130.58 (1$CH_{arom.}$), 127.06, 159.88, 171.04 (3$C_{quat.}$) ppm. IR (KBr): $\tilde{\nu}_{max}$= 3129, 3068, 3008, 2950, 2852, 2133, 2098, 2077, 1612, 1592, 1573, 1499, 1459, 1428, 1253, 1209, 1048, 1021, 947, 908, 880, 810, 764, 690, 673, 649, 559, 493 cm^{-1}. GC-MS (EI) m/z (I, %): 200 (76) *[M]*$^+$, 172 (13), 105 (100), 77 (91), 51 (46). Anal. Calcd for $C_{10}H_8N_4O$: C 59.99; H 4.03; N 27.99. Found C 60.12; H 4.09; N 27.87.

4.4. 3-(Azidomethyl)-5-(p-tolyl)isoxazole ***(10)***

White solid (99 % yield); m.p. 37.5–38.5 °C. 1H NMR (500 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 4.43 (s, 2H, CH_2), 6.49 (s, 1$H_{isox.}$), 7.24 (d, *J* = 7.4 Hz, 2$H_{arom.}$), 7.65 (d, *J* = 7.4 Hz, 2$H_{arom.}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.49 (CH_3), 45.80 (CH_2), 97.95 ($CH_{isox.}$), 125.82 (2$CH_{arom.}$), 129.75 (2$CH_{arom.}$), 124.34, 140.89, 159.78, 171.19 (4$C_{quat.}$) ppm. IR (KBr): $\tilde{\nu}_{max}$= 3136, 3038, 3030, 3008, 2954, 2925, 2864, 2130, 2098, 2077, 1618, 1598, 1566, 1511, 1463, 1455, 1436, 1408, 1378, 1341, 1313, 1252, 1216, 1209, 1114, 1045, 1023, 949, 904, 883, 826, 806, 768, 716, 680, 661, 557, 506 cm^{-1}. GC-MS (EI): m/z (I, %) 214 (100) *[M]*$^+$, 186 (15), 119 (97), 91 (79), 65 (31). Anal. Calcd for $C_{11}H_{10}N_4O$: C 61.67; H 4.71; N 26.15. Found C 61.78; H 4.68; N 26.19.

4.5. General Procedure for the Synthesis of 3-((1H-1,2,3-triazol-1-yl)methyl)-5-arylisoxazoles ***(11–15)***

The mixture of 0.23 mmol $CuSO_4 \cdot 5H_2O$ and 0.45 mmol TBTA in 15 mL MeOH was stirred for 10 min at room temperature and 0.91 mmol Na ascorbate was then added. After stirring for 30 min, the solution of 4.5 mmol isoxazolylazide **9,10** and 4.6 mmol corresponding alkyne (propargyl alcohol, 2-methylbut-3-yn-2-ol, phenyl acetylene) in 15 mL MeOH was added. The reaction mixture was stirred for 4 h and diluted with 150 mL of brine. Precipitate was filtered off, washed with water (3 x 20 mL), dried in vacuum and recrystallized from acetone – CH_2Cl_2 (1 : 1).

4.6. (1-((5-Phenylisoxazol-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methanol ***(11)***

White solid (85 % yield); m.p. 156–157 °C. ^{1}H NMR (500 MHz, DMF-d_7): δ = 4.66 (d, *J* = 5.5 Hz, 2H, CH_2O), 5.25 (t, *J* = 5.5 Hz, 1H, OH), 5.87 (s, 2H, CH_2N), 7.05 (s, 1$H_{isox.}$), 7.49–7.57 (m, 3$H_{arom.}$), 7.86–7.92 (m, 2$H_{arom.}$), 8.19 (s, 1$H_{triazol}$). ^{13}C NMR (125 MHz, DMF-d_7): δ = 45.36 (CH_2N), 55.18 (CH_2O), 100.12 ($CH_{isox.}$), 123.69 ($CH_{triazol}$), 126.17 (2$CH_{arom.}$), 129.74 (2$CH_{arom.}$), 131.10 (1$CH_{arom.}$), 127.40, 149.54, 161.10, 170.85 (4$C_{quat.}$). ^{15}N NMR (50.7 MHz, DMF-d_7): δ = 240 (N^1), 361 (N^2), 372 ($N_{isox.}$). IR (KBr): $\tilde{\nu}_{max}$= 3286, 3139, 3126, 3085, 3058, 2992, 2930, 2883, 1614, 1594, 1576, 1553, 1505, 1468, 1454, 1427, 1372, 1303, 1232, 1137, 1065, 1049, 1039, 1022, 950, 913, 843, 787, 760, 742, 686, 676, 491 cm^{-1}. HPLC-MS, m/z (I, %): 535 *[2M + Na]*$^+$ (19), 279 *[M + Na]*$^+$ (18), 257 *[M + H]*$^+$ (100). Anal. Calcd for $C_{13}H_{12}N_4O_2$: C 60.93; H 4.72; N 21.86. Found C 61.08; H 4.62; N 21.99.

4.7. (1-((5-(p-Tolyl)isoxazol-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methanol ***(12)***

White solid (97 % yield); m.p. 150–152 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.33 (s, 3H, CH_3), 4.56 (d, *J* = 5 Hz, 2H, CH_2O), 5.29 (t, 1H, *J* = 5 Hz, OH,), 5.78 (s, 2H, CH_2N), 6.93 (s, 1 $H_{isox.}$), 7.31 (d, *J* = 8 Hz, 2$H_{arom.}$), 7.73 (d, *J* = 8 Hz, 2$H_{arom.}$), 8.14 (s, 1$H_{triazol}$). ^{13}C NMR (125 MHz, DMSO-d_6): 21.57 (CH_3), 45.24 (CH_2N), 55.62 (CH_2O), 99.74 ($CH_{isox.}$), 124.01 ($CH_{triazol}$), 126.19 (2$CH_{arom.}$), 130.40 (2$CH_{arom.}$), 124.39, 141.21, 149.09, 160.80, 170.65 (5$C_{quat.}$). IR (KBr): $\tilde{\nu}_{max}$= 3289, 3147, 3132, 3123, 3059, 3037, 2992, 2958, 2921, 2853, 1619, 1598, 1568, 1515, 1470, 1436, 1376, 1368, 1319, 1226, 1132, 1116, 1063, 1049, 1038, 1017, 949, 842, 820, 810, 790, 737, 629, 503 cm^{-1}. GC-MS (EI), m/z (I, %): 270 (21) *[M]*$^+$, 242 (24), 119 (100), 91 (59). Anal. Calcd for $C_{14}H_{14}N_4O_2$: C 62.21; H 5.22; N 20.73. Found C 62.40; H 5.03; N 20.66.

4.8. 2-(1-((5-(p-Tolyl)isoxazol-3-yl)methyl)-1H-1,2,3-triazol-4-yl)propan-2-ol ***(13)***

White solid (95 % yield); m.p. 152–153 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.47 (s, 6H, 2CH_3), 2.35 (s, 3H, CH_3), 5.13 (s, 1H, OH), 5.74 (s, 2H, CH_2), 6.95 (s, 1$H_{isox.}$), 7.33 (d, *J* = 8 Hz, 2$H_{arom.}$), 7.75 (d, *J* = 8 Hz, 2$H_{arom.}$), 8.00 (s, 1$H_{triazol}$). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.56 (CH_3), 31.22 (2CH_3), 45.09 (CH_2), 99.82 ($CH_{isox.}$), 121.66 ($CH_{triazol}$), 126.17 (2$CH_{arom.}$), 130.38 (2$CH_{arom.}$), 67.62, 124.36, 141.19, 156.84, 160.71, 170.59 (6$C_{quat.}$). IR (KBr): $\tilde{\nu}_{max}$= 3355, 3129, 3075, 3038, 3001, 2970, 2930, 2874, 1619, 1600, 1568, 1515, 1469, 1441, 1368, 1355, 1301, 1218, 1181, 1135, 1116, 1062, 1047, 1019, 967, 949, 837, 825, 808, 779, 743, 722, 678, 502 cm^{-1}. Anal. Calcd for

$C_{16}H_{18}N_4O_2$: C 64.41; H 6.08; N 18.78. Found C 64.75; H 6.20; N 18.54.

4.9. 5-Phenyl-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)isoxazole ***(14)***

White solid (98 % yield); m.p. 194–195 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.88 (s, 2H, CH_2), 7.07 (s, 1H$_{isox.}$), 7.34 (t, J = 7.4 Hz, 1H$_{arom.}$), 7.45 (t, J = 7.7 Hz, 2H$_{arom.}$), 7.48–7.54 (m, 3H$_{arom.}$), 7.82–7.93 (m, 4H$_{arom.}$), 8.73 (s, 1H$_{triazol}$). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 45.61 (CH_2), 100.38 ($CH_{isox.}$), 122.65 ($CH_{triazol}$), 125.83 (2$CH_{arom.}$), 126.26 (2$CH_{arom.}$), 128.60 (1$CH_{arom.}$), 129.50 (2$CH_{arom.}$), 129.85 (2$CH_{arom.}$), 131.27 (1$CH_{arom.}$), 127.03, 131.10, 147.39, 160.76, 170.58 (5$C_{quat.}$). IR (KBr): $\tilde{\nu}_{max}$= 3122, 3098, 3054, 2999, 2957, 2918, 2850, 1612, 1593, 1574, 1465, 1453, 1440, 1355, 1347, 1227, 1200, 1182, 1076, 1048, 1027, 1011, 973, 947, 912, 830, 786, 764, 749, 685, 507, 490 cm^{-1}. HPLC-MS, m/z (I, %): 303 $[M + H]^+$ (100). Anal. Calcd for $C_{18}H_{14}N_4O$: C 71.51; H 4.67; N 18.53. Found C 71.65; H 4.64; N 18.39.

4.10. 3-((4-Phenyl-1H-1,2,3-triazol-1-yl)methyl)-5-(p-tolyl)isoxazole ***(15)***

White solid (91 % yield); m.p. 178–179 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.33 (s, 3H, CH_3), 5.86 (s, J = 7.4 Hz, 2H, CH_2), 6.99 (s,1H$_{isox.}$), 7.31 (d, J = 8.1 Hz, 2H$_{arom.}$), 7.34 (t, J = 7.4 Hz, 1H$_{arom.}$), 7.45 (t, J = 7.7 Hz, 2H$_{arom.}$), 7.75 (d, J = 8.1 Hz, 2H$_{arom.}$), 7.89 (d, J = 7.2 Hz, 2H$_{arom.}$), 8.73 (s, 1H$_{triazol}$). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.56 (CH_3), 45.62 (CH_2), 99.71 ($CH_{isox.}$), 122.64 ($CH_{triazol}$), 125.83 (2$CH_{arom.}$), 126.20 (2$CH_{arom.}$), 128.59 (1$CH_{arom.}$), 129.49 (2$CH_{arom.}$), 130.38 (2$CH_{arom.}$), 124.38, 131.11, 141.21, 147.39, 160.68, 170.75 (6$C_{quat.}$). IR (KBr): $\tilde{\nu}_{max}$=3108, 3088, 3047, 3032, 2991, 2946, 2917, 2856, 1619, 1597, 1517, 1463, 1440, 1431, 1350, 1223, 1200, 1184, 1117, 1079, 1047, 973, 948, 912, 839, 821, 783, 761, 752, 694, 517, 505 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_4O$: C 72.13; H 5.10; N 17.71. Found: C 72.29; H 5.05; N 17.60.

4.11. 2-(But-3-yn-1-yl)-5-(5-phenylisoxazol-3-yl)-1,3,4-oxadiazole ***(19)***

DCC (0.97 g, 4.7 mmol) was added to a solution of pent-4-inoic acid (0.94 g, 9.58 mmol) in 10 mL anhydrous toluene. The reaction mixture was stirred for 30 min at room temperature, precipitate filtered off, and 3-(1*H*-tetrazol-5-yl)-5-phenylisoxazole **18** (1g, 4.69 mmol) was added to the filtrate. The obtained suspension was refluxed for 6 h, toluene was removed, solid residue washed with chilled toluene, hexane and dried on air to give 0.84 g compound **19** which used without further purification. White solid (86% yield); m.p. 145–147 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.05 (t, 1H, J = 2.5 Hz, ≡CH,), 2.80 (dt, J = 7.2 and 2.5 Hz, 2H, $CH_2\underline{CH_2}C\equiv$), 3.23 (t, 2H, J = 7.2 Hz, $\underline{CH_2}CH_2C\equiv$), 7.15 (s, 1H$_{isox.}$), 7.48–7.54 (m, 3H$_{arom.}$), 7.82–7.87 (m, 2H$_{arom.}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.27 ($CH_2\underline{CH_2}C\equiv$), 25.21 ($\underline{CH_2}CH_2C\equiv$), 70.29 (≡CH), 98.69 ($CH_{isox.}$), 126.22 (2$CH_{arom.}$), 129.39 (2$CH_{arom.}$), 131.26 (1$CH_{arom.}$), 81.06, 126.40, 150.89, 157.77, 166.49, 172.10 (6$C_{quat.}$). IR (KBr): $\tilde{\nu}_{max}$= 3257, 3142, 3068, 3051, 2923, 2853, 2118, 1617, 1607, 1565, 1494, 1470, 1459, 1445, 1428, 1327, 1227, 1119, 1048, 949, 938, 803, 767, 731, 692, 678 cm^{-1}. Anal. Calcd for $C_{15}H_{11}N_3O_2$: C 67.92, H 4.18, N 15.84. Found C 67.84, H 4.09, N 15.94.

4.12. 2-(5-Phenylisoxazol-3-yl)-5-(2-(1-((5(p-tolyl)isoxazol-3-yl)methyl)-1H-1,2,3-triazol-4-yl)ethyl)-1,3,4-oxadiazole ***(20)***

The compound was prepared by the same procedure described for **11–15**, but reaction was carried out at 40 °C. Compound was obtained (91 % yield) as white solid; m.p. 183–184 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.32 (s, 3H, CH_3), 3.22 (t, J = 7.2 Hz, 2H, CH_2,), 3.38 (t, J = 7.2 Hz, 2H, CH_2,), 5.75 (s, 2H, CH_2N), 6.85 (s, 1H$_{isox.}$), 7.30 (d, J = 8 Hz, 2H$_{arom.}$), 7.55–7.61 (m, 3H$_{arom.}$), 7.71 (d, J = 8 Hz, 2H$_{arom.}$), 7.73 (s, 1H$_{isox.}$), 7.95–8.03 (m, 2H$_{arom.}$), 8.10 (s, 1H$_{triazol}$). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.52 (CH_3), 22.45 (CH_2), 25.09 (CH_2), 45.24 (CH_2N), 99.58 ($CH_{isox.}$), 100.05 ($CH_{isox.}$), 123.75 ($CH_{triazol}$), 126.11 (2$CH_{arom.}$), 126.52 (2$CH_{apом.}$), 129.93 (2$CH_{apом.}$), 130.33 (2$CH_{apом.}$), 131.78 (1$CH_{arom.}$), 124.31, 126.37, 141.13, 151.32, 157.21, 160.71, 167.81, 170.57, 171.73 (9$C_{quat.}$). IR (KBr): $\tilde{\nu}_{max}$=3144, 3125, 3116, 3064, 3034, 2992, 2923, 2853, 1619, 1600, 1566, 1493, 1462, 1447, 1427, 1353, 1222, 1120, 1050, 995, 950, 816, 765, 688, 679, 498 cm^{-1}. Anal. Calcd for $C_{26}H_{21}N_7O_3$: C 65.13; H 4.41; N 20.45. Found C 65.27; H 4.75; N 20.51.

4.13. (1-((5-Phenylisoxazol-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl pivalate ***(16)***

Anhydrous Et_3N (0.10 g, 0.99 mmol) was added to a solution of hydroxytriazol-isoxazole **11** (0.23 g, 0.90 mmol) and pivaloyl chloride (0.11 g, 0.91 mmol) in 30 mL anhydrous dichloromethane. The reaction mixture was stirred for 4 h at reflux, diluted with water, acidified with HCl, organic layer separated and dried over sodium sulfate. After removal of the solvent in vacuo 0.30 g ester **16** was obtained which does not need further purification. White solid (99 % yield); m.p. 117–119 °C. ^{1}H NMR (500 MHz, DMF-d_7): δ = 1.13 (s, 9H, 3Me), 5.21 (s, 2H, CH_2O), 5.92 (s, 2H, CH_2N), 7.05 (s, 1H$_{isox.}$), 7.50–7.56 (m, 3H$_{arom.}$), 7.86–7.91 (m, 2H$_{arom.}$), 8.38 (s, 1H$_{triazol}$). ^{13}C NMR (125 MHz, DMF-d_7): δ = 26.96 (3CH_3), 45.53 (CH_2N), 57.99 (CH_2O), 100.11 ($CH_{isox.}$), 125.52 ($CH_{triazol}$), 126.17 (2$CH_{arom.}$), 129.74 (2$CH_{apом.}$), 131.12 (1$CH_{apом.}$), 38.79, 127.38, 143.65, 160.91, 170.90, 177.84 (6$C_{quat.}$). ^{15}N NMR (50.7 MHz, DMF-d_7): δ = 242 (N^1), 355 (N^3), 364 (N^2), 372 ($N_{isox.}$). IR (KBr): $\tilde{\nu}_{max}$= 3118, 3094, 3074, 2981, 2970, 2935, 2874, 1731, 1613, 1593, 1575, 1480, 1468, 1452, 1429, 1396, 1366, 1313, 1283, 1227, 1165, 1154, 1133, 1051, 1037, 1007, 964, 947, 916, 842, 821, 787, 764, 740, 689, 681, 500 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_4O_3$: C 63.52; H 5.92; N 16.46. Found: C 63.75; H 5.88; N 16.35.

4.14. General procedure for the synthesis of $LPdCl_2$ complexes

General procedure for the synthesis of $LPdCl_2$ complexes. 40 mL of 0.025 M solution (1 mmol) of the corresponding ligand (L^{1-7}) in MeOH was added dropwise under stirring to 10 mL of 0.1 M methanol solution of Na_2PdCl_4 (1 mmol), and the mixture was stirred at room temperature. After 10 min, the precipitate was filtered off, washed with water, methanol, and dried in air at room temperature for one day.

4.15. Complex L^1PdCl_2

Pale yellow solid (96 % yield); ^{1}H NMR (500 MHz, DMF-d_7): δ (rotamer1 / rotamer2) = 5.29 / 5.33 (s, 2H, CH_2O), 5.75 (br.s, 1H, OH), 6.01 / 6.04 (s, 2H, CH_2N), 7.10 / 7.12 (s, 1H, $CH_{isox.}$), 7.49–7.66 (m, 3H$_{arom.}$), 7.80–7.95 (m, 2H$_{arom.}$), 8.47 / 8.50 (s, 1H, $CH_{triazol}$). ^{13}C NMR (125 MHz, DMF-d_7): δ = 47.15 / 47.25 (CH_2N), 57.01 / 57.15 (CH_2O), 100.24 ($CH_{isox.}$), 126.16 (2$CH_{arom.}$), 126.33 ($CH_{triazol}$), 129.78 (2$CH_{arom.}$), 131.22 (1$CH_{arom.}$), 127.25, 151.26 / 151.86; 160.00 / 160.06; 171.10 (4$C_{quat.}$). ^{15}N NMR (50.7 MHz, DMF-d_7): δ = 228 / 248 (N^3), 244 (N^1), 354 (N^2), 372 ($N_{isox.}$). IR (KBr): $\tilde{\nu}_{max}$ =3417, 3111, 2988, 2943, 2871, 1610, 1591, 1573, 1607, 1455, 1420, 1340, 1243, 1147, 1093, 1062, 1024, 950, 797, 764, 688, 493 cm^{-1}. HPLC-MS, m/z: 830.942 (calcd for $[M - Cl^-]^+$ 830.905). Anal. Calcd for $C_{26}H_{24}Cl_4N_8O_4Pd_2$: C 36.01; H 2.79; Cl 16.35; N 12.92; Pd 24.54. Found C 36.28; H 3.02; Cl 14.95; N 13.09; Pd 24.38.

4.16. Complex L^2PdCl_2

Pale yellow solid (94% yield); $\tilde{\nu}_{max}$ = 3429, 3132, 3097, 2949, 2922, 1612, 1595, 1476, 1454, 1407, 1161, 1020, 951, 820, 802 cm^{-1}. Anal. Calcd for $C_{14}H_{14}Cl_2N_4O_2Pd$: C 37.57; H 3.15; Cl 15.84; N 12.52; Pd 23.78. Found C 37.41; H 3.25; Cl 15.73; N 12.57; Pd 23.41.

4.17. Complex L^3PdCl_2

Pale yellow solid (91% yield); IR (KBr): $\tilde{\nu}_{max}$ = 3435, 3118, 2976, 2917, 2870, 1614, 1597, 1474, 1369, 1184, 1175, 1124, 1078, 951, 816, 781 cm^{-1}. Anal. Calcd for $C_{16}H_{18}Cl_2N_4O_2Pd$: C 40.40; H 3.81; Cl 14.91; N 11.78; Pd 22.37. Found C 40.47; H 3.97; Cl 15.04; N 11.72; Pd 22.05.

4.18. Complex L^4PdCl_2

Pale beige solid (90% yield); IR (KBr): $\tilde{\nu}_{max}$ = 3119, 3062, 3000, 2951, 1610, 1590, 1574, 1457, 1368, 1342, 1239, 1160, 1114, 1054, 951, 921, 818, 764, 691 cm^{-1}. Anal. Calcd for $C_{18}H_{14}Cl_2N_4O_2Pd$: C 45.07; H 2.94; Cl 14.78; N 11.68; Pd 22.19. Found C 45.17; H 3.16; Cl 14.83; N 11.63; Pd 22.08.

4.19. Complex L^5PdCl_2

Pale beige solid (88 % yield); IR (KBr): $\tilde{\nu}_{max}$ = 3431, 3131, 2920, 2855, 1615, 1598, 1565, 1515, 1488, 1467, 1459, 1441, 1369, 1339, 1331, 1315, 1239, 1206, 1184, 1158, 1111, 1058, 1019, 1004, 949, 822, 762, 744, 695, 503 cm^{-1}. Anal. Calcd for $C_{19}H_{16}Cl_2N_4O_2Pd$: C 46.23; H 3.27; Cl 14.36; N 11.35; Pd 21.56. Found C 46.15; H 3.36; Cl 14.48; N 11.39; Pd 21.41.

4.20. Complex L^6PdCl_2

Yellow solid (67 % yield); ^{1}H NMR (500 MHz, DMF-d_7): δ (rotamer1/rotamer2) = 1.24 / 1.25 (s, 9H, $3CH_3$), 5.73 / 5.78 (s, 2H, CH_2O), 6.06 / 6.08 (s, 2H, CH_2N), 7.09 / 7.11 (s, 1H, $CH_{isox.}$), 7.52–7.56 (m, $3H_{arom.}$), 7.86–7.91 (m, $2H_{arom.}$), 8.70 / 8.73 (s,$1H_{triazol}$). ^{13}C NMR (125 MHz, DMF-d_7): δ (rotamer1 / rotamer2) = 27.09 ($3CH_3$), 47.32 / 47.41 (CH_2N), 57.69 / 57.81 (CH_2O), 100.22 / 100.25 ($CH_{isox.}$), 126.16 ($2CH_{arom.}$), 128.09 / 128.17 ($CH_{triazol}$), 129.79 ($2CH_{arom.}$), 131.24 ($1CH_{arom.}$), 38.98 / 39.01; 127.24; 145.12 / 145.72; 159.85 / 159.88; 171.12; 177.89 ($6C_{quat.}$). ^{15}N NMR (50.7 MHz, DMF-d_7): δ (rotamer1 / rotamer2) = 235 / 253 (N^3), 246 (N^1), 358 (N^2), 373 ($N_{isox.}$). IR (KBr): $\tilde{\nu}_{max}$ = 3442, 3153, 2971, 2933, 2871, 1731, 1611, 1592, 1575, 1457, 1398, 1280, 1147, 1101, 1049, 1035, 951, 803, 766, 690 cm^{-1}. HPLC-MS, m/z: 998.988 (calcd for $[M - Cl]^+$ 999.020). Anal. Calcd for $C_{36}H_{40}Cl_4N_8O_6Pd_2$: C 41.76; H 3.89; Cl 13.70; N 10.82; Pd 20.56. Found C 41.56; H 3.91; Cl 13.64; N 10.90; Pd 20.41.

4.21. Complex L^7PdCl_2

Pale brown solid (88% yield); IR (KBr): $\tilde{\nu}_{max}$ = 3473, 3111,3066, 2947, 2858, 2922, 1614, 1589, 1566, 1464, 1444, 1431, 1400, 951, 766 cm^{-1}. Anal. Calcd for $C_{26}H_{21}Cl_2N_7O_3Pd$: C 47.55; H 3.22; Cl 10.79; N 14.93; Pd 16.20. Found C 47.44; H 3.31; Cl 10.64; N 14.87; Pd 16.01.

4.22. General procedure for the Suzuki-Miyaura reaction

A 20 mL Schlenk tube with a magnetic stir bar was charged with 3-bromobenzoic acid **21** (0.5 mmol), 4-methoxyphenylboronic acid **22** (0.6 mmol), K_2CO_3 (1.25 mmol), 5 ml of solvent [H_2O, H_2O-MeOH (1:1)] and 50 μL of solution ($1{\cdot}10^{-2}$-$1{\cdot}10^{-5}$ M) of palladium complexes $LPdCl_2$ in DMF under air atmosphere. The reaction mixture was placed in a preheated oil bath: at 100 °C for MeOH-H_2O and at 35 °C or 100 °C for H_2O; and stirred for the appropriate time and under conditions required (Tables 4). After this time, the mixture was cooled, diluted with 5 mL of H_2O, 5 mL of Et_2O and acidified by 1 M HCl. The organic phase was separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, concentrated in vacuo and the yield was determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane (0.5 mmol) as internal standard (Tables 4). The pure product was obtained by a simple filtration of ether solution through silica gel pad and evaporation of solvent.

*4.23. 4-Methoxybiphenyl-3-carboxylic Acid **(23)***

White crystalline powder (98 % yield), m.p. 203-204°C (m.p. 202–203 °C[36]). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.79 (s, 3H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.82—7.90 (m, 2H), 8.12 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.2, 114.5, 126.8, 127.5, 127.9, 129.2, 130.6, 131.4, 131.6, 140.2, 159.2, 167.3. IR (KBr): $\tilde{\nu}_{max}$ = 3394, 3081, 2957, 2840, 1678, 1600, 1586, 1423, 1395, 1317, 1289, 1272, 1241, 1197, 1172, 1124, 1062, 1009, 931, 756 cm^{-1}. Calcd for $C_{14}H_{12}O_3$: C 73.67; H 5.30. Found: C 73.69; H 5.37.

4.24. General procedure for the Mizoroki–Heck reaction

A 20 mL Schlenk tube with a magnetic stir bar was charged with 3-iodobenzoic acid **24** (0.5 mmol), acrylic acid **25** (0.75 mmol), K_2CO_3 (1.5 mmol), 5 ml of water and 50 μL of the solution ($1{\cdot}10^{-2}$ M) of palladium complexes $LPdCl_2$ in DMF under air atmosphere. The reaction mixture was placed in a preheated at 100 °C oil bath and stirred for the appropriate time (Tables 5). After this time, the mixture was cooled, diluted with 5 mL of H_2O, 5 mL of EtOAc and acidified by 1 M HCl. The organic phase was separated, and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The yield was determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane (0.5 mmol) as internal standard (Tables 4). The pure product was obtained by a simple filtration of solution through silica gel pad and evaporation of solvent.

*4.25. 3-[(E)-2-carboxyvinyl]benzoic acid **(26)***

White crystalline powder (97 % yield), m.p. 284–285 °C (m.p. 284–286 °C[37]). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.58 (d, *J* = 16.0 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 16.0 Hz, 1H), 7.90-8.00 (m, 2H), 8.14 (s, 1H), 12.81 (br. s, 2H). ^{13}C NMR (100 MHz, DMSO-d6): δ (ppm) = 120.5, 129.0, 129.3, 130.8, 131.6, 132.0, 134.7, 142.9, 166.9, 167.4. Calcd for $C_{10}H_8O_4$: C 62.50; H 4.20; O 33.30. Found: C 62.46; H 4.27.

4.26. General procedure for the Sonogashira reaction

A 20 mL Schlenk tube with a magnetic stir bar was charged with methyl *p*-iodobenzoate **27** (0.5 mmol), prop-2-yn-1-ol **28** (0.65 mmol), triethylamine (1.5 mmol), CuI (0.005 mmol), 4.9 ml of 2-methyltetrahydrofuran, 50 μL of solution ($4{\cdot}10^{-2}$ M) of PPh_3 and 50 μL of solution ($2{\cdot}10^{-2}$ M) of palladium complexes $LPdCl_2$ in 2-MeTHF under argon atmosphere. The reaction mixture was stirred at room temperature for the appropriate time (Tables 6). After this time, the mixture was added to a saturated solution of brine (5 mL). The resulting water-organic phases were separated and the organic phase was dried over Na_2SO_4. The yield was determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane (0.5 mmol) as internal standard (Tables 6). The pure product was obtained by filtration of solution through silica gel pad and evaporation of the solvent under reduced pressure. Removal of solvent was carried out in a closed volume, which allowed carrying out 90-95% regeneration of the solvent.

4.27. Methyl 4-(3-hydroxyprop-1-yn-1-yl)benzoate **(29)**

White crystalline powder (96 % yield), m.p. 83-84°C (m.p. 82–84 °C[38]). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (br.s, 1H), 3.90 (s, 3H), 4.50 (s, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.5, 52.2, 84.9, 90.2, 127.2, 129.5, 129.7, 131.5, 166.5. IR (KBr): $\tilde{\nu}_{max}$ = 3323, 1726, 1430, 1282, 1119, 1031 cm^{-1}. Calcd for for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30; O 25.24. Found: C, 69.39; H, 5.40.

X-ray Crystal Data

CCDC 1823325 contains the supplementary crystallographic data of compound **11** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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