ISSN 1070-4280, Russian Journal of Organic Chemistry, 2019, Vol. 55, No. 9, pp. 1416–1422. © Pleiades Publishing, Ltd., 2019.

Synthesis of Triazole Click Ligands for Suzuki–Miyaura Cross-Coupling of Aryl Chlorides

S. Jabeen[a], R. A. Khera[a],* J. Iqbal[a], and M. Asgher[b]

[a] *Department of Chemistry, University of Agriculture, Faisalabad, Pakistan*
**e-mail: rasheedahmaduaf@yahoo.com*

[b] *Department of Biochemistry, University of Agriculture, Faisalabad, Pakistan*

Received April 24, 2019; revised June 26, 2019; accepted July 2, 2019

Abstract—A series of new triazole ligands has been synthesized via copper-catalyzed cycloaddition reaction of readily available azides and alkynes. The synthesized compounds were characterized by FTIR, ^{1}H and ^{13}C NMR, and high-resolution mass spectra. The ligands provided excellent yields (up to 92%) in the palladium-catalyzed Suzuki–Miyaura cross coupling of unactivated aryl chlorides with phenylboronic acid. 1-Benzyl-4-(2,6-dimethoxyphenyl)-1*H*-1,2,3-triazole was found to be the most effective ligand due to the presence of electron-donating 2,6-dimethoxyphenyl substituent, which made it possible to develop a highly active ligand–catalyst system for the Suzuki reaction of aryl chlorides.

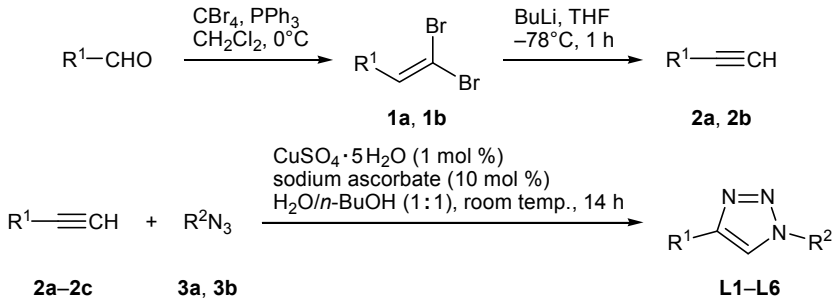
Keywords: triazoles, palladium-catalyzed reaction, Suzuki–Miyaura cross coupling, aryl chlorides, azide–alkyne cycloaddition, click reaction.

DOI: 10.1134/S1070428019090239

Despite the availability of diverse ligands, rapid development of structurally modifiable ligands by efficient synthetic route is still imperative for coupling reactions of relatively inert substrates such as aryl chlorides. Click reaction is an indispensable and versatile methodology which facilitates the practices of organic strategies and provides joining of two building moieties in a facile and energetically favored selective pathway with excellent yield under moderate reaction conditions [1, 2]. Huisgen reaction is an exergonic C–N bond-forming 1,3-dipolar cycloaddition reaction between terminal acetylene and organic azide affording five-membered 1,2,3-triazole derivatives [3]. Sharpless referred this reaction as the cream of the crop in click chemistry and the premier model of a click reaction [4]. However, a drawback of this reaction is that a mixture of regioisomeric 1,4- and 1,5-disubstituted triazoles is always formed. In 2005, Sharpless–Fokin [5–7] and Meldal research groups [8, 9] independently proposed copper-catalyzed addition reaction between organic azides and terminal alkynes producing exclusively 1,4-disubstituted triazoles under mild conditions.

Triazole is a privileged functional group found in several areas of chemistry (bioactive ingredients in drugs) [10, 11], materials science, polymer chemistry, etc. Surprisingly, the role of triazoles as ligands in transition metal catalyzed cross-coupling reactions remains unexplored. Therefore, triazole-based ligand systems have attained significant attention over the past few years owing to their novelty in catalytic systems [12] with distinctive application as directing moiety in C–H bond activation [13, 14] in organometallic chemistry [15–18] and versatile building blocks in organic synthesis [19]. Triazole ring has shown attractive features in terms of most basic donor atom, which made it monodentate ligand [20]. Deprotonated triazole ring via C^3 coordination can also act as monodentate carbanionic ligand [21, 22]. Thus we were interested in exploiting the coordination chemistry of 1,2,3-triazoles toward transition metals since we anticipated that electron-donating substituents at the 1- and 4-positions of the triazole ring would influence their steric and electronic properties that are decisive factors for the coordination with transition metals. The electronic structure of a ligand and its metal complex is an imperative factor for successful catalytic application in cross-coupling reactions. It has also been admitted that ligand plays a significant role in the catalysis because the key factors of catalysis such as reactivity, stability, and selectivity of reaction could be changed by varying electronic and steric properties of the ligand according to reaction conditions or desirability of catalyst [23, 24]. The activation

Scheme 1.



1, **2**, R^1 = 2-$MeOC_6H_4$ (**a**), 2,6-$(MeO)_2C_6H_3$ (**b**); **3**, R^2 = C_8H_{15} (**a**), $PhCH_2$ (**b**); **L1**, R^1 = 2-$MeOC_6H_4$, R^2 = $PhCH_2$; **L2**, R^1 = 2,6-$(MeO)_2C_6H_3$, R^2 = $PhCH_2$; **L3**, R^1 = Ph, R^2 = $PhCH_2$; **L4**, R^1 = 2-$MeOC_6H_4$, R^2 = C_8H_{15}; **L5**, R^1 = 2,6-$(MeO)_2C_6H_3$, R^2 = C_8H_{15}; **L6**, R^1 = Ph, R^2 = C_8H_{15}.

of specific bond in a substrate (C–Cl, C–O, C–I, C–H, C–N, C–Br, etc.) mainly depends upon the nature of metal–ligand complex formed during the catalytic cycle. Therefore, the synthesis of novel ligand is considered the driving force in the success of transition metal-catalyzed cross coupling reactions to improve reaction selectivity under mild reaction conditions. However, some challenges in cross-coupling reactions, e.g., activation of inert substrates, are at the forefront of the search for appropriate ligands in order to carry out the reaction under moderate reaction conditions [25]. Aryl chlorides seem to be good coupling moieties in cross coupling reaction due to their low cost, availability, and diversity [26].

The copper-catalyzed cycloaddition reaction also termed "click reaction" was used to synthesize triazole ligands **L1**–**L6** (Scheme 1). Initial terminal alkynes **2a** and **2b** were prepared by the two-step Corey–Fuchs reaction. Phenylacetylene (**2c**) is a commercially available product. In the first step, 1,1-dibromoolefins **1a** and **1b** were obtained from the corresponding aldehydes, and in the second step, dibromides **1a** and **1b** were treated with *n*-butyllithium in THF [27]. Copper-catalyzed click reaction of terminal alkynes **2a**–**2c** with azides **3a** and **3b** afforded 1,4-disubstituted triazoles **L1**–**L6** in good yields. Several key features, such as no need to protect functional groups, insensitivity to water, and the possibility of working in a broad range of solvent systems, pH, and temperature made this reaction ideal for the synthesis of substituted triazoles as compared to other catalytic reaction. Moreover, there was no need of chromatographic isolation since simple filtration and vacuum drying gave pure products in good yield.

The Suzuki–Miyaura cross-coupling reaction is the most efficient route to access biaryls and substituted aromatics. During the last decade, the application of ligands radically improved the efficacy and selectivity in cross-coupling reactions. Most of the Suzuki coupling reactions catalyzed by Pd–phosphine complexes required excess ligand. However, these phosphine ligands lose their coordinating power to soft metals due to oxidation, and are therefore unsuitable for long-term storage. The synthesized triazole ligands were tested to substitute phosphine ligands in the Suzuki–Miyaura reaction.

Initially, Suzuki cross-coupling of 4-chlorotoluene (**4a**) with phenylboronic acid (**5**) was studied as a model reaction (Scheme 2, Table 1). The reaction was carried out in the presence of 2.5 mol % of $Pd(OAc)_2$, 5 mol % of ligand **L1**–**L6**, and 2 equiv of K_3PO_4 as a base in dioxane at 80°C for 24 h. In all cases, 4-methylbiphenyl (**6a**) was obtained in good yields, and the best yield was achieved using 2,6-dimethoxyphenyl-substituted triazole **L2** (Table 1, entry no. 2). Thus, 1-benzyl-4-(2,6-dimethoxyphenyl)-1*H*-1,2,3-triazole (**L2**) was selected to investigate the effects of the base, solvent, reaction time, temperature, and Pd source on the Suzuki cross-coupling reaction of **4a** and **5**.

Further optimization showed that the base had significant effect on the reaction yield (Table 2).

Scheme 2.

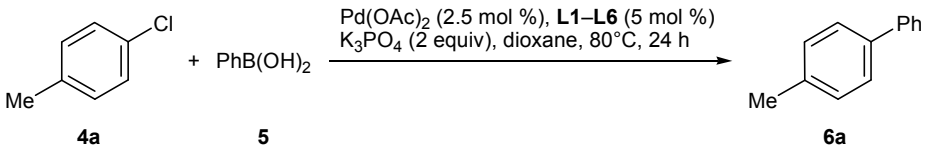


Table 1. Suzuki cross-coupling of 1-chloro-4-methylbenzene (**4a**) with phenylboronic acid (**5**) in the presence of triazole ligands **L1**–**L6**[a]

Entry no.	Ligand	Yield of **6a**,[b] %
1	**L1**	68
2	**L2**	71
3	**L3**	61
4	**L4**	60
5	**L5**	66
6	**L6**	59

[a] Reaction conditions: **4a**, 1.0 mmol; **5**, 1.5 mmol; $Pd(OAc)_2$, 2.5 mol %; ligand **L1**–**L6**, 5 mol %; dioxane, 3 mL; K_3PO_4, 2 mmol; 24 h, 80 °C.

[b] Hereinafter, isolated yield is given.

Table 2. Suzuki cross-coupling of 1-chloro-4-methylbenzene (**4a**) with phenylboronic acid (**5**) in the presence of different bases[a]

Entry no.	Base	Yield of **6a**, %
1	Cs_2CO_3	60
2	KOH	45
3	K_3PO_4	71
4	NaOBu-*t*	75
5	CsF	59
6	KF	55
7	K_2CO_3	68
8	KOBu-*t*	49

[a] Reaction conditions: **4a**, 1.0 mmol; **5**, 1.5 mmol; $Pd(OAc)_2$, 2.5 mol %; ligand **L2**, 5 mol %; dioxane, 3 mL; base, 2 mmol; 24 h, 80 °C.

Table 3. Temperature and solvent effects on the Suzuki cross-coupling of 1-chloro-4-methylbenzene (**4a**) with phenylboronic acid (**5**)[a]

Entry no.	Temperature, °C	Solvent	Yield of **6a**, %
1	60	Dioxane	56
2	80	Dioxane	75
3	60	Toluene	59
4	80	DMF	51
5	80	THF	50
6	100	Toluene	79
7	120	Toluene	35
8	80	Water	35
9	80	Toluene/H_2O	48
10	80	EtOH	43

[a] Reaction conditions: **4a**, 1.0 mmol; **5**, 1.5 mmol; $Pd(OAc)_2$, 2.5 mol %; ligand **L2**, 5 mol %; solvent, 3 mL; NaOBu-*t*, 2 mmol; 24 h.

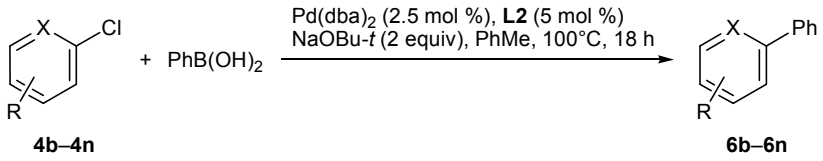
Sodium *tert*-butoxide proved to the best one (yield 75%; Table 2, entry no. 4), though K_3PO_4 also gave a comparable result (71%, entry no. 3). Actually, the base employed in the cross-coupling reaction influences the slow transmetalation step of the catalytic cycle by generating more reactive boronate intermediate [28, 29] and replacing halide ion from the metal coordination sphere [30]. However, the selection of base for cross-coupling reactions is empirical, and no rule has been established for base selection until now.

Temperature optimization experiments showed that the product yield decreased as the temperature was lowered (Table 3). Due to low reactivity of aryl chloride **4a**, the optimal temperature was relatively high (100°C). Further raising the temperature to 120°C reduced the yield because of decomposition of the ligand or product. The reaction yield was surprisingly low in DMF, EtOH, and THF, and toluene was found to ensure the best results (Table 3, entry no. 6), presumably due to solubilization of the reacting species.

Different palladium sources were tested in combination with different reaction times. The reaction with 2 mol % of $Pd(OAc)_2$ afforded only 46% yield of **6a** in 12 h. NMR monitoring of the reaction progress showed the presence of unreacted substrate **4a**. When the reaction time was prolonged to 24 h, the yield increased only to 69% (Table 4, entry no. 5). The palladium source was then changed to $Pd(dba)_2$ and $PdCl_2$ along variation of the reaction time. A good yield of **6a** (81%) was achieved in the presence of $Pd(dba)_2$ in 18 h (Table 4, entry no. 6), whereas increase of the reaction time to 24 h reduced the yield, which may be due to decomposition of the product. Thus the optimum conditions were as follows: $Pd(dba)_2$, 2.5 mol %, as palladium source; 1-benzyl-4-(2,6-dimethoxyphenyl)-1*H*-1,2,3-triazole (**L2**), 5 mol %, as ligand; toluene, 3 mL, as solvent; sodium *tert*-butoxide, 2 equiv, as base; reaction time 18 h; temperature 100°C.

After establishing the optimal conditions, the Suzuki coupling was carried out with a number of aryl chlorides **4b**–**4n** to examine the efficacy of the palladium–ligand catalytic system (Scheme 3, Table 5). The substrate series included activated (Table 5, entry nos. 1–7) non-activated (entry no. 8), and deactivated aryl chlorides (entry nos. 8–13). Aryl chlorides with electron-withdrawing groups give the desired biaryl coupling product in 92–87% yield, and the electron-withdrawing power of the substituent was related to the product yield: NO_2 (92%) > CF_3 (91%) >

Scheme 3.



4b–4n **6b–6n**

For R and X, see Table 5.

CN (90%) > COMe (87%) > CO_2Me (86%) (Table 5, entry nos. 6, 5, 2, 4, and 1, respectively). Substrates with electron-donating groups afforded the corresponding biaryl in a lower yield (84–80%; entry nos. 9–13). Good yields were also obtained with 2-chloropyridine (**4h**) and chlorobenzene (85 and 83%; entry nos. 7 and 8, respectively).

In summary, an effective synthetic route has been developed for the synthesis of a series of 1,4-disubstituted 1,2,3-triazole ligands by copper-catalyzed cycloaddition reaction of azides and terminal acetylenes. The obtained ligands were used in the Pd-catalyzed Suzuki–Miyaura cross-coupling reaction with a series of monohalogenated substrates. More electron-rich and bulkier ligands proved to be more efficient, and up to 92% yield of the coupling product was achieved. 1-Benzyl-4-(2,6-dimethoxyphenyl)-1*H*-1,2,3-triazole (**L2**) was the most efficient in the Suzuki coupling. This new catalytic system offer an exceptional level of reactivity in the Suzuki coupling of unactivated aryl chlorides, which was attributed to the σ-donor nitrogen atom in the ligand.

EXPERIMENTAL

All chemicals and reagents were commercial products which were used as received without purification unless otherwise noted. The solvents were dried, degassed, and distilled before use. All non-aqueous reactions were carried out in a nitrogen atmosphere. The progress of reactions was monitored by TLC on glass plates coated with silica gel F254. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 400 MHz Spectrometer (Germany) using TMS as internal standard. The high-resolution mass spectra (ESI-TOF) were run using an Agilent Technologies MS-TOF 6224 instrument. The IR spectra were recorded on a Bruker IFS 48 spectrometer equipped with a ZnSe ATR accessory. Column chromatography was performed using silica gel (grain size 50–63 μm).

Terminal alkynes 2a and 2b (*general procedure*). The corresponding aromatic aldehyde (2.00 mmol) was added to a solution of triphenylphosphine (2.00 g, 8.00 mmol) and carbon tetrabromide (1.33 g, 4 mmol) in methylene chloride (20 mL), cooled to 0°C, and the mixture was stirred for 1 h at 0°C. The mixture was poured into water, the organic phase was separated, and the aqueous layer was extracted with methylene

Table 4. Effect of the reaction time and palladium catalyst on the Suzuki cross-coupling of 1-chloro-4-methylbenzene (**4a**) with phenylboronic acid (**5**)[a]

Entry no.	[Pd], mol %	Time, h	Yield of **6a**, %
1	$Pd(OAc)_2$, 2.0	12	46
2	$Pd(dba)_2$, 2.0	12	61
3	$Pd(dba)_2$, 2.5	15	67
4	$Pd(OAc)_2$, 2.5	15	56
5	$Pd(OAc)_2$, 2.5	24	69
6	$Pd(dba)_2$, 2.5	18	81
7	$PdCl_2$, 2.5	18	42
8	$PdCl_2$, 2.5	24	38

[a] Reaction conditions: **4a**, 1.0 mmol; **5**, 1.5 mmol; ligand **L2**, 5 mol %; toluene, 3 mL; NaOBu-*t*, 2 mmol; 100°C.

Table 5. Suzuki cross-coupling reaction of various aryl chlorides **4b**–**4n** with phenylboronic acid (**5**)[a]

Entry no.	Substrate no.	X	R	Yield of **6**, %
1	**4b**	CH	4-Ac	87
2	**4c**	CH	4-CN	90
3	**4d**	CH	2-CN	89
4	**4e**	CH	4-CO_2Me	86
5	**4f**	CH	4-CF_3	91
6	**4g**	CH	4-NO_2	92
7	**4h**	N	H	85
8	**4i**	CH	H	83
9	**4j**	CH	4-*t*-Bu	80
10	**4k**	CH	2-Me	80
11	**4l**	CH	2,5-Me_2	84
12	**4m**	CH	2-OMe	83
13	**4n**	CH	4-OMe	82

[a] Reaction conditions: **4b**–**4n**, 1.0 mmol; **5**, 1.5 mmol; ligand **L2**, 5 mol %; toluene, 3 mL; NaOBu-*t*, 2 mmol; 100°C, 18 h.

chloride (3×20 mL). The extracts were combined with the organic phase, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to chromatography (hexane–EtOAc, 8:2) to isolate **1a** or **1b**. The product (0.40 mmol) was dissolved in 8 mL of THF, the solution was cooled to –78°C, and a 2.7 M solution of *n*-butyllithium in hexane (3.20 mmol, 1.18 mL) was added dropwise with stirring. The mixture was stirred for 1 h under argon at –78°C and allowed to warm up to room temperature, and 10% aqueous HCl was added. The mixture was extracted with methylene chloride (3×30 mL), the combined extracts were washed with brine (30 mL), dried with Na_2SO_4, and evaporated under reduced pressure, and the residue was purified by chromatography (hexane–CH_2Cl_2, 5:1) to obtain alkyne **2a** or **2b**.

1-(2,2-Dibromoethenyl)-2-methoxybenzene (1a) was synthesized by reaction of 2-methoxybenzaldehyde (0.68 g, 5.00 mmol) with triphenylphosphine (5.24 g, 20.00 mmol) and carbon tetrabromide (3.31 g, 10.00 mmol) in methylene chloride (50 mL). Yield 1.41 mg (96%), light yellow oil. IR spectrum (neat), ν, cm^{-1}: 1597, 1579, 1484, 1462, 1435, 1289, 1245, 1175, 1162, 1110, 1049, 1026. ^{1}H NMR spectrum, δ, ppm: 7.70 d.d (1H, J = 7.6, 1.5 Hz), 7.60 s (1H), 7.34–7.31 m (1H), 6.97 t (1H, J = 7.6 Hz), 6.88 d (1H, J = 8.3 Hz), 3.84 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 156.8, 133.1, 130.2, 129.4, 124.62, 120.4, 110.7, 88.9.

2-(2,2-Dibromoethenyl)-1,3-dimethoxybenzene (1b) was synthesized by reaction of 2,6-dimethoxybenzaldehyde (0.33 g, 2.00 mmol) with triphenylphosphine (2.00 g, 8.00 mmol) and carbon tetrabromide (1.33 g, 4 mmol) in methylene chloride (20 mL). Yield 86%, white solid. IR spectrum (neat), ν, cm^{-1}: 2959, 2935, 2836, 1585, 1469, 1430, 1305, 1288, 1249, 1197, 1106, 1034. ^{1}H NMR spectrum, δ, ppm: 7.28 t (1H, J = 8.5 Hz), 7.25 s (1H), 6.55 d (2H, J = 8.4 Hz), 3.83 s (6H). ^{13}C NMR spectrum, δ_C, ppm: 157.5, 131.3, 130.2, 114.1, 93.4, 56.0.

1-Ethynyl-2-methoxybenzene (2a). Yield 46 mg (87%), light yellow oil. IR spectrum (neat), ν, cm^{-1}: 3280, 1596, 1576, 1489, 1464, 1434, 1289, 1278, 1250, 1177, 1162, 1109, 1046, 1022. ^{1}H NMR spectrum, δ, ppm: 7.47 d.d (1H, J = 7.5, 1.7 Hz), 7.34–7.30 m (1H), 6.93–6.88 m (2H), 3.91 s (3H), 3.31 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 160.8, 134.4, 130.5, 120.7, 111.4, 110.8, 81.3, 56.0.

1-Ethynyl-2,6-dimethoxybenzene (2b). Yield 71%, white solid. IR spectrum (neat), ν, cm^{-1}: 3271, 2927, 2840, 2103, 1584, 1474, 1432, 1296, 1254, 1109, 1030. ^{1}H NMR spectrum, δ, ppm: 7.26 t (2H, J = 7.5 Hz), 6.55 d (2H, J = 8.5 Hz), 3.90 s (6H), 3.56 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 162.4, 130.5, 103.6, 85.6, 56.4.

1-Azidooctane (3a) was synthesized according to procedure reported in [31, 32]. Sodium azide (488 mg, 7.50 mmol) was added to a solution of 1-bromooctane (966 mg, 5.00 mmol) in DMF (2 mL), and the mixture was stirred for 4 h at room temperature (25°C). The mixture was then diluted with water (20 mL) and extracted with ethyl acetate (3×20 mL). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4, and the solvent was removed to leave **3a** as colorless oil. Yield 760 mg (98%). IR spectrum (neat), ν, cm^{-1}: 2927, 2857, 2091, 1466, 1349, 1259, 1124. ^{1}H NMR spectrum, δ, ppm: 3.25 t (2H, J = 7.0 Hz), 1.62–1.57 m (2H), 1.39–1.27 m (10H), 0.88 t (3H, J = 7.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 51.7, 31.9, 29.3, 29.0, 26.9, 28.8, 22.8, 14.2.

Benzyl azide (**3b**) was commercial product.

1-Benzyl-4-(2-methoxyphenyl)-1*H*-1,2,3-triazole (L1). 1-Ethynyl-2-methoxybenzene (**2a**, 265 mg, 2 mmol) and benzyl azide (266 mg, 2 mmol) were added to a 1:1 water–*tert*-butyl alcohol mixture (8 mL). A freshly prepared 1 M aqueous solution of sodium ascorbate (200 μL, 0.2 mmol) and an aqueous solution of $CuSO_4 \cdot 5H_2O$ (65 μL, 5 mg, 0.02 mmol) were then added in succession, and the mixture was stirred for ~14 h at room temperature (TLC). The mixture was diluted with 30 mL of ice water and kept for 15 min in an ice bath, and the white precipitate was filtered off, thoroughly rinsed with cold water (2×15 mL), and dried under reduced pressure. Yield 474 mg (89%), off-white solid. ^{1}H NMR spectrum, δ, ppm: 8.11 s (1H), 7.58 d (2H, J = 7.4 Hz), 7.42 t (1H, J = 8.5 Hz), 7.34–7.28 m (3H), 7.16 d (1H, J = 7.1 Hz), 7.00–6.94 m (2H), 6.13 s (2H), 3.70 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 159.5, 139.5, 136.7, 131.6, 129.2, 128.5, 128.1, 126.5, 120.3, 109.2, 104.1, 56.1, 54.0. Mass spectrum: m/z 266.1214 $[M + H]^+$. Calculated for $C_{16}H_{16}N_3O$: 266.1217.

Ligands **L2–L6** were synthesized in a similar way.

1-Benzyl-4-(2,6-dimethoxyphenyl)-1*H*-1,2,3-triazole (L2). Yield 540 mg (91%), white solid. ^{1}H NMR spectrum, δ, ppm: 7.88 s (1H), 7.54 d (2H, J = 7.1 Hz), 7.38 t (1H, J = 7.6 Hz), 7.34–7.28 m (3H), 6.61 d (2H, J = 7.1 Hz), 6.10 s (2H), 3.69 s (6H). ^{13}C NMR spectrum, δ_C, ppm: 158.5, 141.9, 138.9, 135.6, 131.9, 128.6, 128.2, 127.6, 105.1, 103.6, 55.3, 52.3. Mass

spectrum: *m*/*z* 296.1317 $[M + H]^+$. Calculated for $C_{17}H_{18}N_3O_2$: 296.1315.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (L3). Yield 420 mg (89%), white solid. ^{1}H NMR spectrum, δ, ppm: 8.14 s (1H), 7.54 d (2H, *J* = 6.9 Hz), 7.46–7.41 m (3H), 7.36–7.29 m (5H), 6.14 s (2H). ^{13}C NMR spectrum, δ_C, ppm: 145.8, 137.0, 136.9, 135.2, 130.6, 130.1, 129.0, 128.5, 127.6, 126.0, 52.1. Mass spectrum: *m*/*z* 236.1109 $[M + H]^+$. Calculated for $C_{15}H_{14}N_3$: 236.1110.

4-(2-Methoxyphenyl)-1-octyl-1*H*-1,2,3-triazole (L4). Yield 527 mg (92%), white solid. ^{1}H NMR spectrum, δ, ppm: 8.19 s (1H), 7.46 d (1H, *J* = 6.6 Hz), 7.34–7.11 m (1H), 6.91 d.d (2H, *J* = 6.7, 15 Hz), 4.22 t (2H, *J* = 7.6 Hz), 3.91 s (1H), 2.43–2.38 m (2H), 2.37 d (2H, *J* = 7.1 Hz), 2.02–1.83 m (2H), 1.49–1.20 m (8H), 0.83 t (3H, *J* = 6.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 159.5, 142.8, 142.5, 131.5, 127.1, 120.2, 109.4, 104.1, 56.1, 51.5, 31.9, 29.4, 26.9, 25.6, 22.9, 14.3. Mass spectrum: *m*/*z* 287.4075 $[M + H]^+$. Calculated for $C_{17}H_{26}N_3O$: 287.4073.

4-(2,6-Dimethoxyphenyl)-1-octyl-1*H*-1,2,3-triazole (L5). Yield 589 mg (93%), white solid. ^{1}H NMR spectrum, δ, ppm: 8.21 s (1H), 7.38 t (1H, *J* = 7.6 Hz), 6.61 d (2H, *J* = 7.4 Hz), 4.01 t (2H, *J* = 7.3 Hz), 3.69 s (6H), 1.95–1.91 m (2H), 1.73–1.58 m (2H), 1.30–1.15 m (8H), 0.81 t (3H, *J* = 6.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 159.5, 143.0, 132.5, 127.09, 111.8, 104.1, 56.3, 51.4, 31.9, 29.4, 26.6, 25.7, 22.7, 14.2. Mass spectrum: *m*/*z* 318.2107 $[M + H]^+$. Calculated for $C_{18}H_{28}N_3O_2$: 318.2105.

1-Octyl-4-phenyl-1*H*-1,2,3-triazole (L6). Yield 469 mg (91%), white solid. ^{1}H NMR spectrum, δ, ppm: 8.24 s (1H), 7.50 d.d (2H, *J* = 6.8, 2.3 Hz), 7.41–7.37 m (3H), 4.55 t (2H, *J* = 7.8 Hz), 2.16–2.09 m (2H), 2.01–1.93 m (2H), 1.36–1.24 m (8H), 0.79 t (3H, *J* = 7.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 150.1, 131.9, 129.7, 129.5, 128.7, 124.6, 51.7, 31.9, 31.8, 29.3, 28.7, 26.8, 22.8, 14.2. Mass spectrum: *m*/*z* 258.1892 $[M + H]^+$. Calculated for $C_{16}H_{24}N_3$: 258.1895.

General procedure for the Suzuki coupling reaction of aryl chlorides 4a–4n with phenylboronic acid (5). A Schlenk tube fitted with a rubber septum was charged with aryl chloride **4a**–**4n** (1.00 mmol), $Pd(dba)_2$ (2.5 mol %), $PhB(OH)_2$ (1.5 mmol, 122 mg), ligand **L2** (5 mol %), and sodium *tert*-butoxide (2.00 mmol, 0.45 g). The mixture was purged three times with argon, freshly distilled toluene (3 mL) was added under argon via a syringe, the rubber septum was replaced with a Teflon cap, and the mixture was stirred in an oil bath at 100°C for 18 h. The progress of the reaction was monitored by TLC until the substrate was completely consumed. After cooling to room temperature, 20 mL of ethyl acetate and 20 mL of brine were added, and the mixture was vigorously stirred in a separatory funnel. The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The extracts were combined with the organic phase, dried over Na_2SO_4, filtered, and concentrated, and the residue was purified by column chromatography on silica gel.

4-Methylbiphenyl (6a). Colorless liquid. ^{1}H NMR spectrum, δ, ppm: 7.61 d (2H, *J* = 7.9 Hz), 7.49 d (2H, *J* = 8.20), 7.40 t (2H, *J* = 8.20 Hz), 7.30 t (1H, *J* = 7.6 Hz), 7.23 d (2H, *J* = 8.17 Hz), 2.38 s (3H).

1-(Biphenyl-4-yl)ethanone (6b). White solid. ^{1}H NMR spectrum, δ, ppm: 8.07 d.d (2H, *J* = 1.4, 7.3 Hz), 7.70 d.d (2H, *J* = 1.6, 7.1 Hz), 7.69–7.64 m (2H), 7.50–7.43 m (3H), 2.60 s (3H).

Biphenyl-4-carbonitrile (6c). Off-white solid. ^{1}H NMR spectrum, δ, ppm: 7.81 d (2H, *J* = 8.4 Hz), 7.70 d (2H, *J* = 8.2 Hz), 7.60 t (2H, *J* = 6.9 Hz), 7.49 t (2H, *J* = 6.7 Hz), 7.41 t (1H, *J* = 7.2 Hz).

Methyl biphenyl-4-carboxylate (6e). White solid. ^{1}H NMR spectrum, δ, ppm: 8.15 d (2H, *J* = 8.5 Hz), 7.71–7.60 m (4H), 7.53–7.46 m (2H), 7.42–7.37 m (1H), 3.93 s (3H).

4-(Trifluoromethyl)biphenyl (6f). Off-white solid. ^{1}H NMR spectrum, δ, ppm: 7.78–7.72 m (4H), 7.69–7.62 m (2H), 7.54–7.41 m (3H).

4-Nitrobiphenyl (6g). Pale yellow solid. ^{1}H NMR spectrum, δ, ppm: 8.31 d (2H, *J* = 8.8 Hz), 7.75 d (2H, *J* = 8.9 Hz), 7.67–7.60 m (2H), 7.55–7.43 m (3H).

2-Phenylpyridine (6h). Off-white solid. ^{1}H NMR spectrum, δ, ppm: 8.69 d (1H, *J* = 5.2 Hz), 8.03 d (2H, *J* = 7.5 Hz), 7.69 d (2H, *J* = 4.3 Hz), 7.50 t (2H, *J* = 7.4 Hz), 7.44 t (1H, *J* = 7.3 Hz), 7.19 d.d (1H, *J* = 4.3, 7.9 Hz).

4-*tert*-Butylbiphenyl (6i). White solid. ^{1}H NMR spectrum, δ, ppm: 7.60 d (2H, *J* = 8.3 Hz), 7.53 t (2H, *J* = 8.5 Hz), 7.46 d (2H, *J* = 7.2 Hz), 7.41 t (1H, *J* = 6.9 Hz), 7.35 d (2H, *J* = 8.6 Hz,), 1.37 s (9H).

2,5-Dimethylbiphenyl (6l). White solid. ^{1}H NMR spectrum, δ, ppm: 7.50–7.46 m (2H), 7.44–7.38 m (3H), 7.25 d (1H, *J* = 8.4 Hz), 7.19–7.13 m (2H), 2.46 s (3H), 2.35 s (3H).

4-Methoxybiphenyl (6n). White solid. ^{1}H NMR spectrum, δ, ppm: 7.65 d (2H, *J* = 7.6 Hz), 7.45 t (2H, *J* = 7.8 Hz), 7.35 t (1H, *J* = 7.6 Hz), 7.29 t (2H, *J* = 7.7 Hz), 6.98 d (2H, *J* = 8.7 Hz) 3.86 s (3H).

ACKNOWLEDGMENTS

Financial support from the Higher Education Commission (HEC) of Pakistan to this project is gratefully appreciated.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

REFERENCES

1. Rostovtsev, V.V., Green, L.G., Fokin, V.V., and Sharpless, K.B., *Angew. Chem., Int. Ed*., 2002, vol. 41, p. 2596. doi 10.1002/1521-3773(20020715)41
2. Bock, V.D., Hiemstra, H., and van Maarseveen, J.H., *Eur. J. Org. Chem*., 2006, vol. 2006, p. 51. doi 10.1002/ejoc.200500483
3. Huisgen, R., Szeimies, G., and Möbius, L., *Chem. Ber*., 1967, vol. 100, p. 2494. doi 10.1002/cber.19671000806
4. Kolb, H.C. and Sharpless, K.B., *Drug Discovery Today*, 2003, vol. 8, p. 1128. doi 10.1016/S1359-6446(03)02933-7
5. Wang, Q., Chan, T.R., Hilgraf, R., Fokin, V.V., Sharpless, K.B., and Finn, M., *J. Am. Chem. Soc*., 2003, vol. 125, p. 3192. doi 10.1021/ja021381e
6. Himo, F., Lovell, T., Hilgraf, R., Rostovtsev, V.V., Noodleman, L., and Sharpless, K.B., *J. Am. Chem. Soc*., 2005, vol. 127, p. 210. doi 10.1021/ja0471525
7. Fokin, V.V. and Matyjaszewski, K., *Organic Chemistry: Breakthroughs and Perspectives*, Ding, K. and Dai, L.-X., Eds., Weinheim: Wiley, 2012, p. 247. doi 10.1002/9783527664801.ch7
8. Meldal, M. and Tornøe, C.W., *Chem. Rev*., 2008, vol. 108, p. 2952. doi 10.1021/cr0783479
9. Tornøe, C.W., Christensen, C., and Meldal, M., *J. Org. Chem*., 2002, vol. 67, p. 3057. doi 10.1021/jo011148j
10. Agalave, S.G., Maujan, S.R., and Pore, V.S., *Chem. Asian J*., 2011, vol. 6, p. 2696. doi 10.1002/asia.201100432
11. Thirumurugan, P., Matosiuk, D., and Jozwiak, K., *Chem. Rev*., 2013, vol. 113, p. 4905. doi 10.1021/cr200409f
12. Duan, H., Sengupta, S., Petersen, J.L., Akhmedov, N.G., and Shi, X., *J. Am. Chem. Soc*., 2009, vol. 131, p. 12100. doi 10.1021/ja9041093
13. Ye, X., He, Z., Ahmed, T., Weise, K., Akhmedov, N.G., and Petersen, J.L., *Chem. Sci*., 2013, vol. 4, p. 3712. doi 10.1039/C3SC51211H
14. Gu, Q., Al Mamari, H. H., Graczyk, K., Diers, E., and Ackermann, L., *Angew. Chem., Int. Ed*., 2014, vol. 53, p. 3868. doi 10.1002/anie.201311024
15. Best, M.D., *Biochemistry*, 2009, vol. 48, p. 6571. doi 10.1021/bi9007726
16. Chow, H.F., Lau, K.N., Ke, Z., Liang, Y., and Lo, C.M., *Chem. Commun*., 2010, vol. 46, p. 3437. doi 10.1039/C0CC00083C
17. Hua, Y. and Flood, A.H., *Chem. Soc. Rev*., 2010, vol. 39, p. 1262. doi 10.1039/B818033B
18. Hein, J.E., and Fokin, V.V., *Chem. Soc. Rev*., 2010, vol. 39, p. 1302. doi:10.1039/B904091A
19. Gulevich, A.V. and Gevorgyan, V., *Angew. Chem., Int. Ed*., 2013, vol. 52, p. 1371. doi 10.1002/anie.201209338
20. Schulze, B. and Schubert, U.S., *Chem. Soc. Rev*., 2014, vol. 43, p. 2522. doi 10.1039/C3CS60386E
21. Nolte, C., Mayer, P., and Straub, B.F., *Angew. Chem., Int. Ed*., 2007, vol. 46, p. 2101. doi 10.1002/anie.200604444
22. Donnelly, K.F., Petronilho, A., and Albrecht, M., *Chem. Commun*., 2013, vol. 49, p. 1145. doi 10.1039/C2CC37881G
23. Miura, M., *Angew. Chem., Int. Ed*., 2004, vol. 43, p. 2201. doi 10.1002/anie.200301753
24. Christmann, U. and Vilar, R., *Angew. Chem., Int. Ed*., 2005, vol. 44, p. 366. doi 10.1002/anie.200461189
25. Kumbhar, A., *J. Org. Chem*., 2017, vol. 848, p. 22. doi 10.1016/j.jorganchem.2017.07.009
26. Littke, A.F., and Fu, G.C., *Angew. Chem., Int. Ed*., 2002, vol. 41, p. 4176. doi 10.1002/1521-3773(20021115)41:22<4176::AID-ANIE4176>3.0.CO;2-U
27. Yoshimura, N., Momotake, A., Shinohara, Y., Nishimura, Y., and Arai, T., *Chem. Lett*., 2008, vol. 37, p. 174. doi 10.1246/cl.2008.174
28. Kürti, L., and Czakó, B., *Strategic Applications of Named Reactions in Organic Synthesis*, Amsterdam: Elsevier, 2005.
29. Braga, A.A., Morgon, N.H., Ujaque, G., and Maseras, F., *J. Am. Chem. Soc*., 2005, vol. 127, p. 9298. doi 10.1021/ja050583i
30. Miyaura, N., *J. Organomet. Chem*., 2002, vol. 653, p. 54. doi 10.1016/S0022-328X(02)01264-0
31. Maury, J., Feray, L., Bertrand, M.P., Kapat, A., and Renaud, P., *Tetrahedron*, 2012, vol. 68, p. 9606. doi 10.1016/j.tet.2012.09.066
32. Ngai, M.H., Yang, P.Y., Liu, K., Shen, Y., Wenk, M.R., and Yao, S.Q., *Chem. Commun*., 2010, vol. 46, p. 8335. doi 10.1039/C0CC01276A