# Di(1*H*-benzo[*d*][1,2,3]triazol-1-yl)methane: An efficient ligand for copper and amine-free palladium-catalysed Sonogashira coupling reaction

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Abstract. An efficient Pd-catalysed Sonogashira coupling reaction was achieved in the absence of copper and amine with inorganic base using phosphene-free, air stable di(1H-benzo[d][1,2,3]triazol-1-yl)methane as ligand. The cross coupling of electron-rich, electron-deficient and hindered aryl halides with terminal alkynes afforded the internal alkynes in good to excellent yields.

Keywords. Palladium; terminal alkynes; benzotriazole; amine-free; copper-free.

#### 1. Introduction

Transition metal-catalysed reactions play an important role in the synthesis of various organic substrates, natural products and pharmaceutically viable molecules.<sup>1</sup> Among all the metals, palladium has emerged as a powerful tool<sup>2</sup> for the cross coupling reaction like Heck, Negishi, Suzuki and Sonogashira coupling reactions.<sup>3</sup> The conjugated  $\pi$  systems resulting from alkynylation reactions are building blocks often encountered within natural products, pharmaceutical molecules, synthetic agrochemicals, and molecular materials.<sup>4,5</sup> During last decade Sonogashira reaction has become one of the most widely used method for the synthesis of aryl or vinyl acetylenes from aryl or vinyl halides and terminal alkynes.

Many applications of Sonogashira coupling of aryl halides with terminal alkynes have been reported in the literature since 1975.<sup>5,6</sup> A large number of efforts have been directed to explore new catalytic systems. The most common catalytic system for this reaction is the combination of palladium and phosphines such as PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>/PPh<sub>3</sub>, and Pd(PPh<sub>3</sub>)<sub>4</sub> with CuI as the co-catalyst and amines as the solvents under degassed condition.7 Successful examples include replacement of triphenylphosphine with some special phosphines to enhance the catalytic efficiency.<sup>8</sup> However, many phosphine ligands are airsensitive and expensive, resulting in significant limits on their synthetic applications.<sup>9</sup> Furthermore, the presence of CuI can result in the formation of some Cu(I) acetylides in situ that can readily undergo oxidative homocoupling reaction of acetylenes.<sup>10</sup> To overcome these drawbacks, many phosphine and copper-free palladium-catalysed Sonogashira coupling protocols have been developed.<sup>11</sup> Recently a copper-free Sonogashira cross-coupling reaction was reported using combination of phosphine and amine along with large amount of tetra-n-butyl ammonium salt as an activator.<sup>12a,c</sup> Recently, Mino et al. described hydrazone ligands for such cross-coupling.<sup>12b</sup> Development of an efficient, inexpensive, copper-, phosphine- and aminefree catalytic system is considerable. In continuation of our efforts on the designing of benzotriazole based ligands for the coupling reactions, and synthetic elaboration of heterocycles by using palladiumcatalysed coupling reactions, <sup>13a-h</sup> here we are reporting Di(1H-benzo[d][1,2,3]triazol-1-yl)methane (L4) as new air-stable and phosphine-free ligand for palladium-catalysed Sonogashira cross-coupling reaction without using copper and amine (scheme 1).

## 2. Experimental

# 2.1 General procedure for Sonogashira cross-coupling reaction of terminal alkynes with aryl halides

A flask was charged with  $Pd(OAc)_2$  (3 mol%), L4 (6 mol%) and 1.0 mmol of aryl halide in 1.5 mL of DMSO. After stirring at room temperature for 15 min, terminal alkyne (1.5 equiv.) and  $K_2CO_3$  (2.5 equiv.) were added to the flask, and the reaction mixture was stirred at 80°C for 10–12 h. After completion of

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Scheme 1. Sonogashira coupling reaction using di(1H-benzo[d][1,2,3]triazol-1-yl) methane (L4).

reaction as indicated by thin-layer chromatography (TLC), water (10 mL) was added to the reaction mixture. It was then extracted with ethyl acetate (2  $\times$  10 mL). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and was concentrated under reduced pressure. The crude was then purified by column chromatography on silica gel (100–200 mesh) using petroleum ether/ethyl acetate (98:2) as eluent to afford the desired pure products.

## 3. Results and discussion

Firstly, with the above precedents in mind, in order to optimize the reaction conditions we undertook an intensive screening of variety of ligands and reaction variables. We first chose electron-rich p-bromoanisole (2a) and penylacetylene (1a) as model reaction to screen the catalyst systems to optimize the reaction conditions. Initially, a series of ligands, benzotriazole and its

	≡ + Br-	∕−ome _	Pd/L	$ \rightarrow = -\langle $	OMe	
1a 2a			За			
Entry	Solvent	Temp	Ligand	Base	Yield	
		(°C)	(L)		(%) <sup>b</sup>	
1	DMF	80	L1	K <sub>2</sub> CO <sub>3</sub>	38	
2	DMF	80	L2	$K_2CO_3$	45	
3	DMF	80	L3	$K_2CO_3$	20	
4	DMF	80	L4	$K_2CO_3$	85	
5	DMF	60	L4	$K_2CO_3$	62	
6	DMF	80	L4	$Na_2CO_3$	45	
7	DMF	80	L4	pyridine	trace	
8	DMF	80	L4	Et <sub>3</sub> N	65	
9	DMF	80	L4	$Cs_2CO_3$	78	
10	DMF	80	L4	KOH	trace	
11	DMF	80	L4	KOt Bu	trace	
12	CH <sub>3</sub> CN	80	L4	$K_2CO_3$	68	
13	Dioxane	80	L4	$K_2CO_3$	38	
14	DME	80	L4	$K_2CO_3$	60	
15	DMA	80	L4	$K_2CO_3$	75	
16	DMSO	80	L4	K <sub>2</sub> CO <sub>3</sub>	90	
Z,Z Z,H Z,H		, ́N ́́СН₂ОН І		N=N		
L1	L2		L3	L	4	

 Table 1. Optization of Sonogashira reaction conditions.<sup>a</sup>

<sup>a</sup>Reaction conditions: 1.0 mmol of 1-bromo-4-methoxybenzene **2a**, 1.5 mmol of phenylacetylene **1a**, 2.5 equiv. of base, 3 mol% of Pd(OAc)<sub>2</sub>, 6 mol% of ligand and 1.5 mL of solvents. <sup>b</sup>Isolated yield

derivatives (L1–L4) were examined (table 1, entries 1–4). It was found that without ligand less than 10% of the desired cross-coupling product **3a** was obtained, along with 40% homo-coupling product of the phenylacety-

lene. The addition of benzotriazole (L1) enhanced the yield of the coupling product 3a up to 38% (table 1, entry 1). In order to achieve the best results in cross-coupling reaction, three derivatives of benzotriazole,

	<ul><li>√</li><li>√</li><li>×</li><li>+</li></ul>	R <sup>2</sup>	3 mol% Pd(OAc) <sub>2</sub> 6 mol% L4	—P2	
	R <sup>1</sup> 2	1a-e	DMSO, K <sub>2</sub> CO <sub>3,</sub> 80 °C R <sup>1</sup>	3	
Entry	Aryl halide		Product	Yiel	ld (%) <sup>b</sup>
1	MeO-	2a	MeO-	3a	90°
2	MeOBr	2b		<b>3</b> a	88
3	Me	2c	MePh	3b	86 <sup>c</sup>
4	MeBr	2d		3b	82
5	⟨Br	2e	Ph	3c	84
6	Br	<b>2</b> f	BrPh	3d	81 <sup>c</sup>
7	MeOC — Br	2g	MeOCPh	3e	87
8	O <sub>2</sub> N-Br	2h	O <sub>2</sub> N-	3f	92
9	Br	2i	Ph	3g	80
10	OMe Br MeO	2j	OMe Ph MeO	3h	80
11	OHCBr	2k	OHCPh	3i	86
12		21		3j	84
13		2a	MeO-	3k	82
14		2c	Me-	31	81
15		21	Et	3m	81
16	Me	2m	Me-	3b	45 <sup>d</sup>

Table 2. Pd/L4 catalysed cross-coupling reaction of alkynes with aryl halides.<sup>a</sup>

<sup>a</sup>Reaction conditions: 1.0 mmol of aryl halides, 1.5 mmol of terminal alkyne, 2.5 equiv. of  $K_2CO_3$ , 3 mol% of Pd(OAc)<sub>2</sub>, 6 mol% of Ligand L4, and 1.5 mL of DMF at 80°C, 10–12 h. <sup>b</sup>Isolated yield. <sup>c</sup>Reaction was carried out at 80°C for 2–4 h. <sup>d</sup>Reaction was carried out at 110°C for 15 h.



having more electron density and probable binding site, 1-H-benzotriazolylmethanol L2, 1-((1H-imidazol-1yl)methyl)-1*H*-benzo[d][1,2,3]triazole L3, and di(1Hbenzo[d][1,2,3]triazol-1-yl)methane L4, were tested as ligands and were found more effective than ligand L1 in the cross-coupling reaction (table 1, entries 2, 3, and 4). It was observed that in a series of reactions with 3 mol% of Pd(OAc)<sub>2</sub> and 6 mol% of ligand L2, L3 and L4 in DMF at 80°C using 2.5 equiv K<sub>2</sub>CO<sub>3</sub>, coupling product 3a was obtained in 45, 20 and 85% yields respectively (table 1, entries 2, 3 and 4). Product 3a was obtained in 62% yield at 60°C (table 1, entry 5). It is evident from the table 1 that ligand L4 was found more effective than ligand L1, L2 and L3. A significant effect of bases was found in the reaction. When Na<sub>2</sub>CO<sub>3</sub> was used as a base **3a** was obtained only in 45% yield (table 1, entry 6). Pyridine was found ineffective; however Et<sub>3</sub>N afforded the coupling product in 65% yield under these reaction conditions (table 1, entries 7 and 8). Cs<sub>2</sub>CO<sub>3</sub> afforded the coupling product in 78% yield (table 1, entry 9). With strong bases such as KOH and KOtBu, trace amount of the coupling product was obtained (table 1, entries 10 and 11). It can be observed from the table 1 that amongst the bases tested (table 1, entries 4, 6–11),  $K_2CO_3$  was found most suitable and amongst various solvents DMSO was proved to be the best solvent (table 1, entries 4, 12–16).

Subsequently, selected terminal alkynes **1a–d**, were reacted with various aryl iodides and bromides **2a–l** under the optimized reaction conditions (table 2). All the aryl halides with electron-releasing and electron-withdrawing groups were successfully coupled with terminal alkynes and afforded the corresponding cross-coupling products in 80–92% yields. It is noteworthy that a variety of functional groups (nitro, keto, bromo, and aldehydic) substituted aryl halides tolerate the reaction condition, and afforded the coupling products in good yields in short reaction time using low catalyst loading (3 mol%).

It is interesting to note that the reaction of aryl iodides with 2a, were very rapid at high temperature (80°C) and gave excellent yields of the desired products in 2–4 h (table 2, entries 1, 3, and 6), while the substituted alkynes **1b–d**, having electron releasing

	Br + R	2	4 mol% Pd(OAc) <sub>2</sub> 8 mol% L4 DMSO, K <sub>2</sub> CO <sub>3</sub> , 80 °C	-==-R <sup>2</sup>	
	4	1		5	
Entry	Alkynes		Product	Yie	ld (%) <sup>b</sup>
1	MeO	1e	MeO-	5a	79
2		1a	Br	5b	82
3	Me <sub>2</sub> N-	1b	Me <sub>2</sub> N-	5c	80
4	OMe	1f	OMe Br	5d	60
5	H <sub>2</sub> N	1g		5e	65

Table 3. Pd/L4 catalysed selective cross-coupling reaction of alkynes with o-iodo-bromobenzene.<sup>a</sup>

<sup>a</sup>Reaction conditions: 1.0 mmol of 1-bromo-2-iodobenzene, 1.5 mmol of terminal alkyne, 2.5 equiv. of  $K_2CO_3$ , 4 mol% of Pd(OAc)<sub>2</sub>, 8 mol% of Ligand L4, and 1.5 mL of DMSO at 80°C for 8 h. <sup>b</sup>Isolated yield.



Scheme 2. Sonogashira coupling reaction of 1-(2-iodophenyl)-1*H*-indole 6a–b.

substituent, afforded the desired coupling products in longer duration (table 2, entries 12–16). The efficacy of the catalyst system was also tested on aryl chloride **2m**, and it was found that the reaction of aryl chloride with **1a** gave the desired product **3a** in 45% yield at 110°C after 15 h.

Furthermore, the optimized combination of  $Pd(OAc)_2$  and L4 was further tested with 1-bromo-2iodobenzene 4 and terminal alkynes **1a–b**, **1e–g**. It is evident from the table 3 that the reaction outcome was not much affected by the steric hindrance derived from the *ortho*-substituents (table 3, entries 4 and 5).

Having the results on coupling of aryl halides and 1-bromo-2-iodobenzene benzenes in our hand, we further investigated the coupling of more difficult and large molecules 1-(2-iodophenyl)-1*H*-indoles **6a–b** as shown in scheme 2. Fortunately, the results indicated that the present catalyst system also displayed the high catalytic activity to catalyse the cross-coupling of terminal alkynes **1a–c** with 1-(2-iodophenyl)-1*H*-indole **6a–b** using 5 mol% of Pd(OAc)<sub>2</sub>, 10 mol% of L4 and afforded the coupling products **7a–e** in 76–80% yields at 110°C.

# 4. Conclusion

In summary, we have developed a general method for rapid Sonogashira cross-coupling reaction of aryl halides with terminal alkynes using  $Pd(OAc)_2$ and di(1*H*-benzo[*d*][1,2,3]triazol-1-yl)methane (**L4**) as new air stable and inexpensive ligand. The advantage of this protocol includes omission of copper, easy handling of catalyst and high catalytic activity for electronpoor as well as electron-rich aryl halides under mild and convenient conditions. Further investigations to expand the scope of the designed ligands are ongoing and will be reported in due course.

## **Supporting information**

Characterization data and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of all the synthesized compounds are given as electronic supporting information (see *www.ias.ac.in/chemsci*).

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