

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

JASPAL SINGH and AKHILESH KUMAR VERMA*

Synthetic Organic Chemistry Research Laboratory, Department of Chemistry, University of Delhi,
Delhi 110007, India
e-mail: averma@acbr.du.ac.in

Abstract. An efficient Pd-catalysed Sonogashira coupling reaction was achieved in the absence of copper and amine with inorganic base using phosphine-free, air stable di(1*H*-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.¹ Among all the metals, palladium has emerged as a powerful tool² for the cross coupling reaction like Heck, Negishi, Suzuki and Sonogashira coupling reactions.³ The conjugated π systems resulting from alkynylation reactions are building blocks often encountered within natural products, pharmaceutical molecules, synthetic agrochemicals, and molecular materials.^{4,5} 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.^{5,6} 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 PdCl₂(PPh₃)₂, PdCl₂/PPh₃, and Pd(PPh₃)₄ 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.⁸ However, many phosphine ligands are air-sensitive and expensive, resulting in significant limits on their synthetic applications.⁹ Furthermore, the presence of CuI can result in the formation of some Cu(I) acetylides *in situ* that can readily undergo oxidative

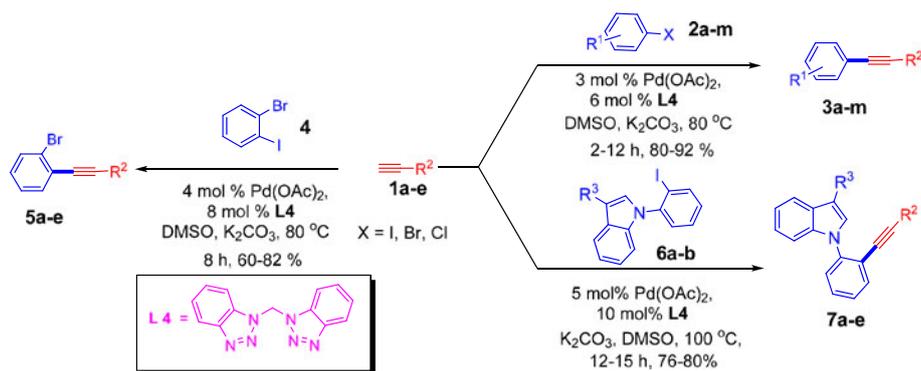
homocoupling reaction of acetylenes.¹⁰ To overcome these drawbacks, many phosphine and copper-free palladium-catalysed Sonogashira coupling protocols have been developed.¹¹ Recently a copper-free Sonogashira cross-coupling reaction was reported using combination of phosphine and amine along with large amount of tetra-*n*-butyl ammonium salt as an activator.^{12a,c} Recently, Mino *et al.* described hydrazone ligands for such cross-coupling.^{12b} Development of an efficient, inexpensive, copper-, phosphine- and amine-free 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 palladium-catalysed coupling reactions,^{13a–h} here we are reporting Di(1*H*-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 K₂CO₃ (2.5 equiv.) were added to the flask, and the reaction mixture was stirred at 80°C for 10–12 h. After completion of

*For correspondence



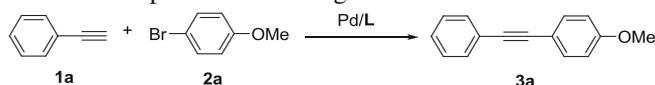
Scheme 1. Sonogashira coupling reaction using di(1*H*-benzo[*d*][1,2,3]triazol-1-yl)methane (**L4**).

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 × 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄ 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.

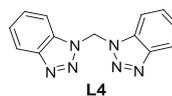
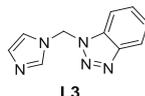
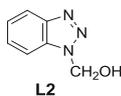
3. Results and discussion

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 phenylacetylene (**1a**) as model reaction to screen the catalyst systems to optimize the reaction conditions. Initially, a series of ligands, benzotriazole and its

Table 1. Optimization of Sonogashira reaction conditions.^a



Entry	Solvent	Temp (°C)	Ligand (L)	Base	Yield (%) ^b
1	DMF	80	L1	K ₂ CO ₃	38
2	DMF	80	L2	K ₂ CO ₃	45
3	DMF	80	L3	K ₂ CO ₃	20
4	DMF	80	L4	K ₂ CO ₃	85
5	DMF	60	L4	K ₂ CO ₃	62
6	DMF	80	L4	Na ₂ CO ₃	45
7	DMF	80	L4	pyridine	trace
8	DMF	80	L4	Et ₃ N	65
9	DMF	80	L4	Cs ₂ CO ₃	78
10	DMF	80	L4	KOH	trace
11	DMF	80	L4	KOtBu	trace
12	CH ₃ CN	80	L4	K ₂ CO ₃	68
13	Dioxane	80	L4	K ₂ CO ₃	38
14	DME	80	L4	K ₂ CO ₃	60
15	DMA	80	L4	K ₂ CO ₃	75
16	DMSO	80	L4	K₂CO₃	90



^aReaction 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)₂, 6 mol% of ligand and 1.5 mL of solvents. ^bIsolated 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-

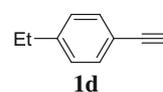
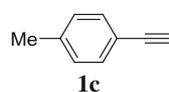
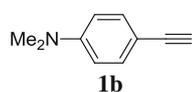
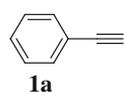
lene. The addition of benzotriazole (**L1**) enhanced the yield of the coupling product **3a** up to 38% (table 1, entry 1). In order to achieve the best results in cross-coupling reaction, three derivatives of benzotriazole,

Table 2. Pd/**L4** catalysed cross-coupling reaction of alkynes with aryl halides.^a

Entry	Aryl halide	Product	Yield (%) ^b
1	2a	3a	90 ^c
2	2b	3a	88
3	2c	3b	86 ^c
4	2d	3b	82
5	2e	3c	84
6	2f	3d	81 ^c
7	2g	3e	87
8	2h	3f	92
9	2i	3g	80
10	2j	3h	80
11	2k	3i	86
12	2l	3j	84
13	2a	3k	82
14	2c	3l	81
15	2l	3m	81
16	2m	3b	45 ^d

^aReaction conditions: 1.0 mmol of aryl halides, 1.5 mmol of terminal alkyne, 2.5 equiv. of K_2CO_3 , 3 mol% of $Pd(OAc)_2$, 6 mol% of Ligand **L4**, and 1.5 mL of DMF at 80°C, 10–12 h.

^bIsolated yield. ^cReaction was carried out at 80°C for 2–4 h. ^dReaction was carried out at 110°C for 15 h.



having more electron density and probable binding site, 1-*H*-benzotriazolylmethanol **L2**, 1-((1*H*-imidazol-1-yl)methyl)-1*H*-benzo[*d*][1,2,3]triazole **L3**, and di(1*H*-benzo[*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)₂ and 6 mol% of ligand **L2**, **L3** and **L4** in DMF at 80°C using 2.5 equiv K₂CO₃, 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 Na₂CO₃ was used as a base **3a** was obtained only in 45% yield (table 1, entry 6). Pyridine was found ineffective; however Et₃N afforded the coupling product in 65% yield under these reaction conditions (table 1, entries 7 and 8). Cs₂CO₃ afforded the coupling product in 78% yield (table 1, entry 9). With strong bases such as KOH and KO^{*t*}Bu, 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), K₂CO₃ was found most suitable and amongst various solvents DMSO was proved to be the best solvent (table 1, entries 4, 12–16).

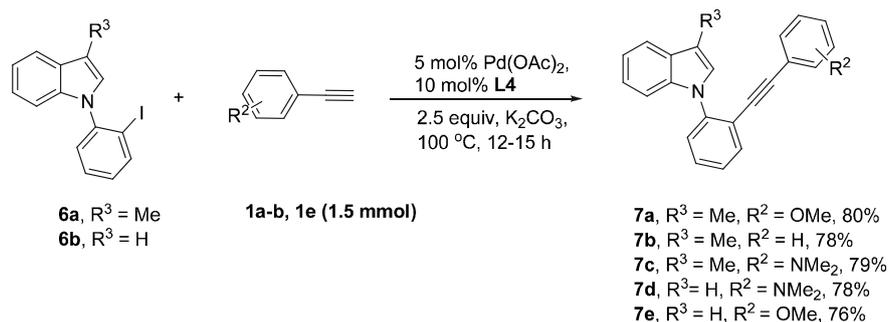
Subsequently, selected terminal alkynes **1a–d**, were reacted with various aryl iodides and bromides **2a–l** under the optimized reaction conditions (table 2). All the aryl halides with electron-releasing and electron-withdrawing groups were successfully coupled with terminal alkynes and afforded the 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

Table 3. Pd/**L4** catalysed selective cross-coupling reaction of alkynes with *o*-iodobromobenzene.^a

Entry	Alkynes	Product	Yield (%) ^b
1	 1e	 5a	79
2	 1a	 5b	82
3	 1b	 5c	80
4	 1f	 5d	60
5	 1g	 5e	65

^aReaction conditions: 1.0 mmol of 1-bromo-2-iodobenzene, 1.5 mmol of terminal alkyne, 2.5 equiv. of K₂CO₃, 4 mol% of Pd(OAc)₂, 8 mol% of Ligand **L4**, and 1.5 mL of DMSO at 80°C for 8 h. ^bIsolated 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-2-iodobenzene **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)₂, 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 electron-poor 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 ¹H and ¹³C NMR spectra of all the synthesized compounds are given as electronic supporting information (see www.ias.ac.in/chemsci).

Acknowledgements

We gratefully acknowledge the Department of Science and Technology (DST), Council of Scientific and Industrial Research (CSIR), New Delhi, and University of Delhi, Delhi for the financial support. JS is thankful to CSIR, for the SRF.

References

- Reviews on transition metal catalysed reactions, see: (a) Magano J and Dunetz J R 2011 *Chem. Rev.* **111** 2177 and references cited therein; (b) Chen X, Engle K M, Wang D and Yu J Q 2009 *Angew. Chem. Int. Ed.* **48** 5094; (c) Ackermann L, Vicente R and Kapdi A R 2009 *Angew. Chem. Int. Ed.* **48** 9792; (d) Nakamura I and Yamamoto Y 2004 *Chem. Rev.* **104** 2127; (e) Gladysz J A 2011 *Chem. Rev.* **111** 1167
- (a) Martin R and Buchwald S L 2008 *Acc. Chem. Res.* **41** 1461; (b) Fu G C 2008 *Acc. Chem. Res.* **41** 1555; (c) Chinchilla R and Njera C 2007 *Chem. Rev.* **107** 874; (d) Molnar A 2011 *Chem. Rev.* **111** 2251; (e) Islam S M, Mondal P, Tuhinab K and Roya A S 2010 *J. Chem. Technol. Biotechnol.* **85** 999 and references cited therein
- (a) Suzuki A 2011 *Angew. Chem. Int. Ed.* **50** 6722; (b) Negishi E I 2011 *Angew. Chem. Int. Ed.* **50** 6738; (c) Wu X F, Anbarasan P, Neumann H and Beller M 2010 *Angew. Chem. Int. Ed.* **49** 9047; (d) Niphakis M J and Georg G I 2011 *Org. Lett.* **13** 196; (e) Ioannidou H A, Kizas C and Koutentis P A 2011 *Org. Lett.* **13** 3466; (f) Proutiere F and Schoenebeck F 2011 *Angew. Chem. Int. Ed.* **50** 8192
- (a) Paterson I, Davies R D M and Marquez R 2001 *Angew. Chem. Int. Ed.* **40** 603; (b) Yoshimura F, Kawata S and Hirama M 1999 *Tetrahedron Lett.* **40** 8281; (c) Graham A E, McKerrecher D, Davies D H and Taylor R J K 1996 *Tetrahedron Lett.* **37** 7445; (d) Nicolaou K C and Dai W M 1991 *Angew. Chem. Int. Ed. Engl.* **30**

- 1387; (e) Maier M E 1995 *Synlett*. Issue 1 13; (f) Grisom J W, Gunawardena G U, Kingberg D and Huang D 1996 *Tetrahedron* **52** 6453; (g) Bunz U H F 2000 *Chem. Rev.* **100** 1605; (h) Tour J M 2000 *Acc. Chem. Res.* **33** 791; (i) Brunsveld L, Meijer E W, Prince R B and Moore J S 2001 *J. Am. Chem. Soc.* **123** 7978
5. For reviews, see the following: (a) Sonogashira, K. In *Metal-catalyzed cross-coupling reactions* 1998; F Diederich and P J Stang (eds); New York: Wiley-VCH; Chapter 5; pp 203; (b) Doucet H and Hierso J C 2007 *Angew. Chem. Int. Ed.* **46** 834; (c) Chinchilla R and Najera C 2007 *Chem. Rev.* **107** 874; (d) Negishi E I and Anastasia L 2003 *Chem. Rev.* **103** 1979
6. (a) Sonogashira K, Tohda Y and Hagihara N 1975 *Tetrahedron Lett.* **16** 4467; (b) Cassar L 1975 *J. Organomet. Chem.* **93** 253; (c) Dieck H A and Heck F R 1975 *J. Organomet. Chem.* **93** 259
7. For selected papers on the palladium/phosphine/CuI/amine system for the Sonogashira cross-coupling reactions, see: (a) Thorand S and Krause N 1998 *J. Org. Chem.* **63** 8551; (b) Hundertmark T, Litter A F, Buchwald S L and Fu G C 2000 *Org. Lett.* **2** 1729; (c) Hierso J C, Fihri A, Amardeil R and Meunier P 2004 *Org. Lett.* **6** 3473; (d) Novák Z, Szabó A, Répási J and Kotschy A 2003 *J. Org. Chem.* **68** 3327; (e) Son S U, Jang Y, Park J, Na H B, Park H M, Yun H J, Lee J and Hyeon T 2004 *J. Am. Chem. Soc.* **126** 5026; (f) Adjabeng G, Brenstrum T, Frampton C S, Robertson A J, Hillhous J, McNulty J and Capretta A 2004 *J. Org. Chem.* **69** 5082; (g) Elangovan A, Wang Y H and Ho T I 2003 *Org. Lett.* **5** 1841; (h) Remmele H, Köllhofer A and Plenio H 2003 *Organometallics* **22** 4098; (i) Batey R A, Shen M and Lough A 2002 *Org. Lett.* **4** 1411; (j) Lee D H, Jung J Y and Jin M J 2010 *Green. Chem.* **12** 2024; (k) Roy S and Plenio H 2010 *Adv. Synth. Catal.* **352** 1014
8. For selected papers on Pd/Ligand and copper free conditions (a) Choudary B M, Madhi S, Chowsari N S, Kantam M L and Sreedhar B 2002 *J. Am. Chem. Soc.* **124** 14127; (b) Herrmann W A 2002 *Angew. Chem., Int. Ed.* **41** 1290; (d) Najera C, Gil-Moltó J, Karlström S and Falvello L R 2003 *Org. Lett.* **5** 1451; (e) Soheili A, Albanese-Walker J, Murry J A, Dormer P G and Hughes D L 2003 *Org. Lett.* **5** 4191; (f) Rau S, Lamm K, Goerls H, Schoeffel J and Walther D 2004 *J. Organomet. Chem.* **689** 3582; (h) Alonso D A, Botella L, Najera C and Pacheco M C 2004 *Synthesis* **10** 1713; (j) Wolf C and Lerebours R 2004 *Org. Biomol. Chem.* **22** 161; (l) Fukuyama T, Shinmen M, Nishitani S, Sato M and Ryu I 2002 *Org. Lett.* **4** 1691; (m) Böhm V P and Hermann W A 2000 *Eur. J. Org. Chem.* Issue 22 3679; (n) Méry D, Heuzé K and Astruc D 2003 *Chem. Commun.* Issue 15 1934; (o) Najera C, Gil-Moltó J, Karlström S and Falvello L R 2003 *Org. Lett.* **5** 1451; (p) Alonso D A, Najera C and Pacheco M C 2003 *Adv. Synth. Catal.* **345** 1146; (q) Ngassa F N, Gomez J M, Haines B E, Ostach M J, Hector J W, Hoogenboom L J and Page C E 2010 *Tetrahedron* **66** 7919; (r) Chen H J, Lin Z Y, Li M Y, Lian R J, Xue Q W, Chung J L, Chen S C and Chen Y J 2010 *Tetrahedron* **66** 7755; (s) Fleckenstein C A and Plenio H 2008 *Green. Chem.* **10** 563; (t) Islam S M, Mondal P, Roy A S, Mondal S and Hossain D 2010 *Tetrahedron Lett.* **51** 2067; (u) Kuang Y Y and Chen F E 2009 *Helv. Chim. Acta* **92** 897
9. Pignolet L H (ed) 1983 *Homogeneous catalysis with metal phosphine complexes*, New York; Plenum
10. (a) Siemsen P, Livingston R C and Diederich F 2000 *Angew. Chem. Int. Ed.* **39** 2632; (b) Li J H, Liang Y and Zhang X D 2005 *Tetrahedron* **61** 1903
11. (a) Li J H, Zhang X D and Xie Y X 2005 *Eur. J. Org. Chem.* Issue 20 4256; (b) Liang Y, Xie Y X and Li J H 2006 *J. Org. Chem.* **71** 379; (c) Yi C and Hua R 2006 *J. Org. Chem.* **71** 2535
12. (a) Liang B, Dai M, Chen J and Yang Z 2005 *J. Org. Chem.* **70** 391; (b) Mino T, Shirae Y, Saito T, Sakamoto M and Fujita T 2006 *J. Org. Chem.* **71** 9499; (c) Komaromi A and Novak Z 2008 *Chem. Commun.* Issue 40 4968 and references therein
13. (a) Verma A K, Singh J, Sankar V K, Chaudhary R and Chandra R 2007 *Tetrahedron Lett.* **48** 4207; (b) Verma A K, Singh J and Chaudhary R 2007 *Tetrahedron Lett.* **48** 7199; (c) Verma A K, Kesharwani T, Singh J, Tandon V and Larock R C 2009 *Angew. Chem., Int. Ed.* **39** 2632; (d) Verma A K, Singh J and Larock R C 2009 *Tetrahedron* **65** 8434; (e) Jha R R, Chaudhary R, Chandra R and Verma A K 2011 *J. Indian Chem. Soc.* **88** 1; (f) Verma A K, Rustagi V, Aggarwal T and Singh A P 2010 *J. Org. Chem.* **75** 7691; (g) Verma A K, Joshi M and Singh V P 2011 *Org. Lett.* **13** 1630; (h) Verma A K, Shukla S P, Singh J and Rustagi V 2011 *J. Org. Chem.* **76** 5670