



Efficient synthesis of [1,2,3]triazolo[5,1-c][1,4]benzoxazines through palladium–copper catalysis

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ARTICLE INFO

Article history:

Received 22 January 2009

Revised 12 March 2009

Accepted 17 March 2009

Available online 21 March 2009

Keywords:

[1,2,3]Triazolo[5,1-c][1,4]benzoxazines

1-Azido-2-(prop-2-ynoxy)benzene

1,3-Cycloaddition

Palladium

Copper

ABSTRACT

A wide variety of [1,2,3]triazolo[5,1-c][1,4]benzoxazines were synthesized through palladium-copper catalyzed reactions of 1-azido-2-(prop-2-ynoxy)benzene with aryl/vinyl iodides. A plausible reaction mechanism has also been proposed.

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Because of the widespread applications of structurally novel heterocycles in drug development, the establishment of new synthetic methods for such molecules has been one of the frontier areas in organic synthesis. In particular, synthetic approaches to various nitrogen- and oxygen-containing heterocycles have been extensively pursued in search of pharmaceutical leads and therapeutic agents. Toward this end, various palladium-catalyzed heteroannulation strategies, especially the addition of nitrogen or oxygen across the triple/double bonds have become very popular.¹ In recent past, triazole derivatives have received considerable attention due to their applications ranging from medicinal chemistry² to material science.³ Fused triazoles endowed with wide range of bioactivities⁴ are also interesting and some of them (e.g., *Estazolam*, *Alprazolam*, etc.) have achieved both clinical and commercial success.⁵ Parallel to these, 1,4-benzoxazines and their dihydro derivatives are frequently found in naturally occurring compounds⁶ and pharmacologically active substances⁷ including drugs^{7c} (e.g., *Levofloxacin*). More importantly, 2,3-dihydro-1,4-benzoxazines fused with triazole have featured in novel therapeutic agents as reported in patents⁸ and utilized for structure based design of fungicides through molecular modeling studies.⁹

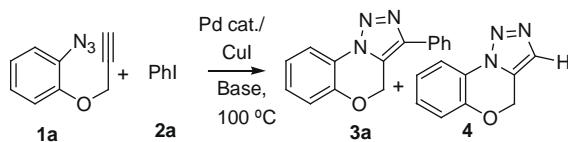
While there are many synthetic routes toward individual 1,4-benzoxazines¹⁰ and 1,2,3-triazoles,¹¹ only a few traditional synthetic methods are available for the synthesis of [1,2,3]triazolo[5,1-c][1,4]benzoxazines.^{8a,12} Some of these involve multi-step procedure with attendant poor overall yields, while others require

harsh and/or sluggish reaction conditions. Moreover, reported methods have been targeted toward the synthesis of some specific [1,2,3]triazolo[5,1-c][1,4]benzoxazine derivatives and thus are limited in general synthetic utility. To the best of our knowledge, modern palladium-catalyzed reactions have completely been ignored to develop a general method for the synthesis of [1,2,3]triazolo[5,1-c][1,4]benzoxazines.

Recently, inter and intramolecular version of azide-alkyne cycloadditions in the presence of transition-metal catalysts has emerged as useful tools in chemical synthesis¹³ and chemical biology¹⁴ as well. In continuation of our efforts in the area of palladium-catalyzed reactions^{7a,15} to develop heterocyclic compounds of biological interest, we have recently reported¹⁶ isoindoline-fused triazoles through successful exploration of intramolecular [3+2] cycloaddition reactions. As a promising extension of our previous study, we felt that O-propargylation of 2-azido phenol and its subsequent reaction with aryl/vinyl halides under palladium-copper catalysis could result in the ultimate formation of 1,4-benzoxazines fused with 1,2,3-triazole, provided appropriate reactions and catalysts could be developed. Herein, we wish to report the preliminary results obtained so far toward this goal.

The reactions of 1-azido-2-(prop-2-ynoxy)benzene **1a** with iodobenzene **2a** were chosen as a model system (Table 1). Initially, we attempted to adopt our previously reported reaction protocol¹⁶ [Pd(PPh₃)₂Cl₂/CuI/Et₃N/DMF/115 °C] to synthesize the targeted product **3a** but to our surprise, **3a** was formed only with 35% yield. This disappointing result prompted screening studies (a selection of which given in Table 1) in order to improve the yield of **3a** and deserves some comments in this context. We ran the reactions

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Table 1Optimization of the reaction conditions for the reaction of iodobenzene (**2a**) with 1-azido-2-(prop-2-ynoxy)benzene (**1a**)^a

Entry	Catalyst system	Co-catalyst	Base (h)	Time ^b (h)	Yield ^c 3a (%)	Yield ^c 4 (%)
1 ^d	Pd(PPh ₃) ₂ Cl ₂	CuI	Et ₃ N	11	37	44
2	Pd(PPh ₃) ₂ Cl ₂	CuI	K ₂ CO ₃	4	45	0
3 ^e	Pd(PPh ₃) ₄	CuI	K ₂ CO ₃	4	27	0
4 ^e	Pd(PPh ₃) ₄	—	K ₂ CO ₃	4	15	35
5	Pd(OAc) ₂ /PPh ₃	CuI	Et ₃ N	4	49	0
6	Pd(OAc) ₂ /PPh ₃	CuI	K ₂ CO ₃	4	64	0
7 ^e	Pd(OAc) ₂ /PPh ₃	—	K ₂ CO ₃	9	37	4
8 ^e	Pd(OAc) ₂	CuI	K ₂ CO ₃	4	0	5
9 ^e	Pd/C	CuI	K ₂ CO ₃	4	0	10

^a Acetylene **1a** (0.57 mmol), phenyl iodide **2a** (0.48 mmol), palladium catalyst (0.024 mmol), CuI (0.048 mmol, except entries 4 and 7), PPh₃ (0.10 mmol, entries 5–7 only), K₂CO₃ (0.72 mmol) or Et₃N (0.72 mmol) in DMF (4 mL, except entry 1).

^b Total experimental time that includes time for stirring at rt followed by heating at 100 °C for 2 h.

^c Chromatographically isolated yield of pure product.

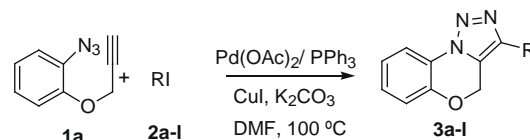
^d Et₃N was used as solvent as well as base.

^e Except the products **3a** and/or **4**, no other significant side products were observed indicating the propensity of starting materials to undergo substantial degradation under the reaction conditions.

through modification of our previously reported protocol¹⁶ with increased catalyst loading and manipulation of other parameters (Table 1, entry 1). For example, treatment of azide **1** (0.57 mmol) and iodobenzene **2a** (0.48 mmol) in the presence of 5 mol % of Pd(PPh₃)₂Cl₂ (0.024 mmol) and 10 mol % of CuI (0.048 mmol) in Et₃N (solvent and base) with stirring at room temperature for 9 h (until consumption of starting materials) followed by heating at 100 °C for 2 h led to the isolation of **3a** (37%) along with 44% of product **4**, a self cycloaddition product of **1a**. Use of stronger base¹⁷ such as K₂CO₃ in DMF resulted in slight improvement of the yield of **3a**, along with complete suppression of formation of the undesired product **4** (Table 1, entry 2). Replacing the catalyst by Pd(PPh₃)₄ with and without CuI furnished the product **3a** with 27% and 15% yields, respectively (Table 1, entries 3 and 4). Employing Pd(OAc)₂ combined with PPh₃ as catalytic system and CuI as co-catalyst and also using Et₃N base in DMF afforded the product **3a** with 49% yield (Table 1, entry 5). Gratifyingly, changing the base to K₂CO₃ afforded a good yield of desired product of **3a** (Table 1, entry 6). Removal of either CuI or PPh₃ resulted in low yield or no formation of product **3a** (Table 1, entries 7 and 8), indicating that their cooperative assistance was crucial for the reaction to proceed. Switching to Pd/C and PPh₃ as catalytic system did not produce any desired product **3a** (Table 1, entry 9). Several other reaction parameters were also tuned. DMF was found to be the solvent of choice among various solvents examined.

Shorter reaction time and lower temperature resulted in incomplete conversion. Immediate heating without stirring at room temperature for requisite time gave lower yields of desired products.

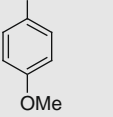
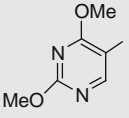
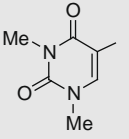
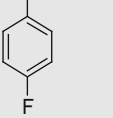
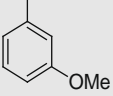
With optimized conditions (Table 1, entry 6) in hand, the scope of the reaction was explored by treating various aryl iodides **2a–l** with 1-azido-2-(prop-2-ynoxy)benzene **1a**. The results are summarized in Table 2. All the products were characterized by spectral and analytical data. In addition, unequivocal conformation of the structure of a representative product **3d** was obtained through X-ray diffraction analysis¹⁸ (Fig. 1). It is obvious that a wide variety of aryl, heteroaryl, and vinyl iodides possessing different functional groups reacted successfully. Unfortunately, aryl bromides did not react. Entries **4–12** in Table 2 showed the compatibility of reaction with different functional groups (e.g., ester, nitro, fluoro, trifluoro, methoxy, methyl, etc.). Apparently, an electron-withdrawing

Table 2Palladium-copper catalyzed synthesis of [1,2,3]Triazolo[5,1-c][1,4]benzoxazines **3a**

Entry	R	Product ^b	Yield ^c (%)
1		3a	64
2		3b	69
3		3c	75
4 ^d		3d	38
5		3e	42
6		3f	70
7		3g	43

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Table 2 (continued)

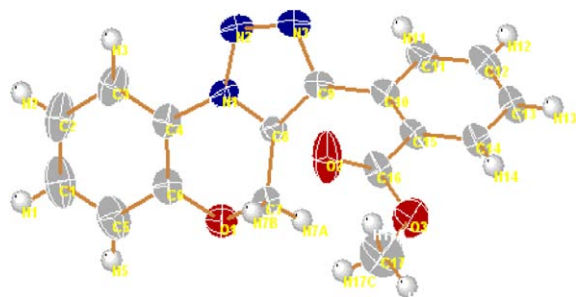
Entry	R	Product ^b	Yield ^c (%)
8		3h	47
9		3i	54
10		3j	56
11		3k	52
12		3l	67

^a The mixture of 1-azido-2-(prop-2-ynoxy)benzene **1a** (0.57 mmol), aryl iodide **2** (0.48 mmol), 5 mol % Pd(OAc)₂ (0.024 mmol), 21 mol % PPh₃ (0.10 mmol), 10 mol % CuI (0.048 mmol), K₂CO₃ (0.72 mmol) in DMF (4 mL) was stirred at rt for 2 h, then heated at 100 °C for another 2 h.

^b Satisfactory spectroscopic (NMR, IR, mass) and analytical data were obtained for all compounds.

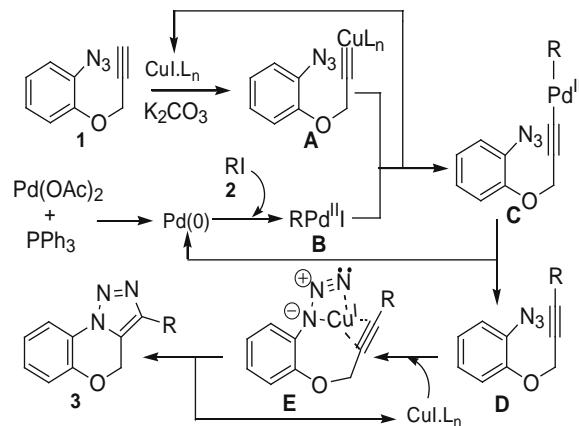
^c Chromatographically isolated yield of pure product.

^d A major part of the starting materials was converted to a tar within 1 h resulting in low yield of the desired product **3d** and no other side product was observed.

Figure 1. Perspective view of compound **3d**.

group present in para-position in iodides **2** (Table 2, entries 6 and 11) facilitated the reaction compared to electron-donating groups (Table 2, entries 7 and 8).

A possible reaction mechanism can be shown as envisaged in Scheme 1. Mechanistically, a copper-acetylide **A** is formed from azide-acetylene **1** with the assistance of copper iodide and base. Thereafter, oxidative addition of aryl (or vinyl) iodides **2** to palladium(0) (generated in situ from Pd(OAc)₂ and PPh₃)¹⁹ leads to σ -aryl (or vinyl) palladium(II) complex **B**.^{20a,b} Next, complex **B** undergoes transmetalation^{20c} through the organocopper species **A** to afford the intermediate species **C**, which upon reductive elimination of Pd(0) generates²¹ internal alkyne **D**. Presumably, **D** is



Scheme 1. Proposed reaction mechanism.

smoothly converted²² to the desired cyclized product **3** through copper-coordinated intermediate species **E**. DMF may also facilitate the cycloadditions as it is a dipolar aprotic solvent.²³

In conclusion, we have developed an efficient and general method for the synthesis of [1,2,3]triazolo[5,1-c][1,4]benzoxazines in one-pot, from readily available starting materials. This method operates through carbon-carbon bond formation followed by intramolecular cycloaddition of aromatic azide with internal alkyne, generated in situ under palladium-copper catalysis. In spite of the widespread popularity of 'click reaction', it is limited to terminal alkynes only. To broaden the scope, several transition-metal-catalyzed cycloadditions between internal alkyne and azide are now being reported.²⁴ In this context, our method adds one more successful example in this area. We believe that it should find applications in medicinal chemistry.

Acknowledgments

A.S. thanks CSIR, India for the award of fellowship and C.C. thanks Director, IICB for his support.

References and notes

- For reviews: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644; (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079; (c) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113; (d) *Metal Catalyzed Cross Coupling Reactions*; Meijere, A. D., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
- (a) Lee, T.; Cho, M.; Ko, S.-Y.; Youn, H.-J.; Baek, D. J.; Cho, W.-J.; Kang, C.-Y.; Kim, S. J. *Med. Chem.* **2007**, *50*, 585; (b) Xia, Y.; Fan, Z.; Yao, J.; Liao, Q.; Li, W.; Qu, F.; Peng, L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2693; (c) De Clercq, E. *Nat. Rev. Drug Disc.* **2002**, *1*, 13.
- (a) Fournier, D.; Hoogenboom, R.; Schubert, U. S. *Chem. Soc. Rev.* **2007**, *36*, 1369; (b) Nandivada, H.; Jiang, X.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197; (c) Evans, R. A. *Aust. J. Chem.* **2007**, *60*, 384; (d) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249; (e) Dondoni, A. *Chem. Asian J.* **2007**, *2*, 700; (f) Gil, M. V.; Arevalo, M. J.; Lopez, O. *Synthesis* **2007**, 1589, and references cited therein.
- (a) Lauria, A.; Patella, C.; Dattolo, G.; Almerico, A. M. *J. Med. Chem.* **2008**, *51*, 2037; (b) Martinez, A.; Gutierrez-de-Teran, H.; Brea, J.; Ravina, E.; Loza, M. I.; Cadavid, M. I.; Sanz, F.; Vidal, B.; Segarra, V.; Sotelo, E. *Bioorg. Med. Chem.* **2008**, *16*, 2103; (c) Nasr, M.; Nasr, A. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *335*, 389; (d) Braccio, M. D.; Grossi, G.; Ceruti, M.; Rocco, F.; Loddò, R.; Sanna, G.; Busonera, B.; Murreddu, M.; Marongiu, M. E. *Il Farmaco* **2005**, *60*, 113.
- (a) Thomas, A. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1881; (b) Broggini, G.; Molteni, G.; Terraneo, A.; Zecchi, G. *Tetrahedron* **1999**, *55*, 14803.
- (a) Mason, J. J.; Bergman, J.; Janosik, T. *J. Nat. Prod.* **2008**, *71*, 1447; (b) Nagao, T.; Otsuka, H.; Kohda, H.; Sato, T.; Yamasaki, K. *Phytochemistry* **1985**, *24*, 2959; (c) Otsuka, H.; Hirai, Y.; Nagao, T.; Yamasaki, K. *J. Nat. Prod.* **1988**, *51*, 74; (d) Hartenstein, H.; Sicker, D. *Phytochemistry* **1994**, *35*, 827; (e) Sainsbury, M. Oxazine, Thiazines and their Benzoderivatives. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p 995.
- For a recent review see (a) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett* **2004**, 2449; (b) Matsuoka, H.; Ohi, N.; Mihara, M.; Suzuki, H.; Miyamoto, K.; Maruyama, N.; Tsuji, K.; Kato, N.; Akimoto, T.; Takeda, Y.;

- Yano, K.; Kuroki, T. *J. Med. Chem.* **1997**, *40*, 105; (c) Mitscher, L. A.; Sharma, P. N.; Chu, D. T. W.; Shen, L. L.; Pernet, A. G. *J. Med. Chem.* **1987**, *30*, 2283; (d) Zhen, Y.; Ming, X.; Yu, B.; Otani, T.; Saito, H.; Yamada, Y. *J. Antibiot.* **1989**, *42*, 1294; (e) Yoshida, K.-I.; Minami, Y.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett.* **1993**, *34*, 2637. and see also Ref. 10a.
8. (a) Bentley, J.; Bergauer, M.; Bertani, B.; Biagetti, M.; Borriello, M.; Bromidge, S. M.; Gianotti, M.; Granci, E.; Leslie, C. P.; Pasquarello, A.; Zucchelli, V. PCT Patent Appl. 2006, WO 2006024517; *Chem. Abstr.* **2006**, *144*, 254134u.; (b) Georgiev, S.; Loev, B.; Musser, J. US Patent 1981, US 4,276,292; *Chem. Abstr.* **1981**, *95*, 132905v.
9. Jordan, D. B.; Basarab, G. S.; Liao, D.-I.; Johnson, W. M. P.; Winzenberg, K. N.; Winkler, D. A. *J. Mol. Graphics Modell.* **2001**, *19*, 434.
10. For a recent review see (a) Ilas, J.; Anderluh, P. S.; Dolenc, M. S.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325; (b) Banik, B. K.; Samajdar, S.; Banik, I. *Tetrahedron Lett.* **2003**, *44*, 1699; (c) Bartsch, H.; Ofner, M.; Schwarz, O.; Thomann, W. *Heterocycles* **1984**, *22*, 2789; (d) Albanese, D.; Landini, D.; Penso, M. *Chem. Commun.* **1999**, 2095; (e) Heine, H. W.; Schairer, W. C.; Sariano, J. A.; William, E. A. *Tetrahedron* **1988**, *44*, 3181; (f) Atkinson, J.; Morand, P.; Arnason, T. *J. Org. Chem.* **1991**, *56*, 1788. and see also Ref. 7a.
11. (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565; (b) Harvey, G. R. *J. Org. Chem.* **1966**, *31*, 1587; (c) Augusti, R.; Kascheres, C. *J. Org. Chem.* **1993**, *58*, 7079; (d) Journet, M.; Cai, D.; Kowal, J. J.; Larsen, R. D. *Tetrahedron Lett.* **2001**, *42*, 9117; (e) Harju, K.; Vahermo, M.; Mutikainen, I.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2003**, *5*, 826; (f) Alajarin, M.; Cabrera, J.; Pastor, A.; Villalgorido, J. M. *Tetrahedron Lett.* **2007**, *48*, 3495.
12. (a) Fusco, R.; Garanti, L.; Zecchi, G. *J. Org. Chem.* **1975**, *40*, 1906; (b) Tsuge, O.; Ueno, K.; Inaba, A. *Heterocycles* **1976**, *4*, 1; (c) Medaer, B. P.; Van Aken, K. J.; Hoornaert, G. *J. Tetrahedron* **1996**, *52*, 8813.
13. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2596; (b) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998; (c) Chandrasekhar, S.; Rao, C. L.; Nagesh, C.; Reddy, C. R.; Sridhar, B. *Tetrahedron Lett.* **2007**, *48*, 5869; (d) Miljanic, O.; Dichtel, W. R.; Mortezaei, S.; Stoddart, J. F. *Org. Lett.* **2006**, *8*, 4835; (e) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237.
14. (a) Link, A. J.; Vink, M. K. S.; Tirrel, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 10598; (b) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046; (c) Sawa, M.; Hsu, T.-L.; Itoh, T.; Sugiyama, M.; Hanson, S. R.; Vogt, P. K.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 12371; (d) Nakane, M.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2008**, *73*, 1842; (e) Dedola, S.; Nepogodiev, S. A.; Field, R. A. *Org. Biomol. Chem.* **2007**, *5*, 1006. and references cited therein.
15. (a) Chowdhury, C.; Kundu, N. G. *Chem. Commun.* **1996**, 1067; (b) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863; (c) Chaudhuri, G.; Chowdhury, C.; Kundu, N. G. *Synlett* **1998**, 1273; (d) Kundu, N. G.; Mahanty, J. S.; Chowdhury, C.; Dasgupta, S. K.; Das, B.; Spears, C. P.; Baljarini, J.; De Clercq, E. *Eur. J. Med. Chem.* **1999**, *34*, 389.
16. Chowdhury, C.; Mondal, S. B.; Achari, B. *Tetrahedron Lett.* **2005**, *46*, 8531.
17. K₂CO₃ and Et₃N found to be superior amongst other bases (inorganic and organic) tested.
18. Compound **3d** was crystallized by slow evaporation from hexanes:ethyl acetate (95:5); Crystal data: C₁₇H₁₃N₃O₃, *M* = 307.30, triclinic, space group P1̄, *a* = 6.8601(4) Å, *b* = 10.1112(6) Å, *c* = 12.0728(7) Å, *V* = 741.57(8) Å³, *Z* = 2, *D*_{calcd} = 1.376 Mg m⁻³, *T* = 296(2) K, *μ* = 0.097 mm⁻¹, *F*(000) = 320, *λ* = 0.71073 Å, Processed reflections 15,535 and unique reflections 3374, Final *R* factor = 0.0527. The crystal data has been deposited at Cambridge Crystallographic Data Centre [CCDC No. 715006]. Copies of the data can be obtained free of charge via www.ccdc.ac.uk/conts/retrieving.html or CCDC, 12 union Road, Cambridge CB2 1EZ, UK.
19. MaCrindle, R.; Ferguson, G.; Arsenaault, G. J.; McAlees, A. J.; Stephenson, D. K. *J. Chem. Res., Synop.* **1984**, 360.
20. (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46; (b) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874; (c) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.
21. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
22. Internal alkyne **D** (R = Ph) was isolated and several control experiments were carried out under various reaction conditions. Among them, desired cycloaddition took place smoothly when alkyne **D** was heated in DMF at 100 °C for 2 h in the presence of 10 mol % of copper(I) iodide.
23. Kadaba, P. K. *J. Org. Chem.* **1976**, *41*, 1073.
24. (a) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680; (b) Kamijo, S.; Jin, T.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 689; (c) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923.