Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 5221–5224

Tetrahedron Letters

A mild and efficient palladium-catalyzed homocoupling of lithium alkynyltriisopropoxyborates: a new route to synthesis of 1,3-diynes

Chang Ho Oh* and V. Raghava Reddy

Department of Chemistry, Hanyang University, Sungdong–Gu, Seoul 133-791, South Korea

Received 12 April 2004; revised 2 May 2004; accepted 10 May 2004

Abstract—Lithium alkynyltriisopropoxyborates were homocoupled in the presence of palladium acetate and DPEPhos. This protocol allows a new efficient route to synthesis of 1,3-diynes under very mild conditions.

Palladium-catalyzed coupling reactions are very efficient and reliable procedures for the construction of new carbon–carbon bonds.[1] In particular, Sonogoshira reaction has used extensively over the past three decades for the elaboration of arylalkynes. The reaction is a straightforward way to achieve arylalkynyl derivatives, although 1,3-diynes are formed as by-products.[2] The prominent occurrence of biologically active compounds containing conjugated 1,3-diynes continues to encourage the devolpment of new strategies for their rapid and efficient synthesis.[3] Among the various approaches,[4] the use of organometalic reagents such as organosilanes,[5] organoantimony,[6] and organotin[7] have attracted much attention. However, many of these organometalic reagents and their by-products are highly toxic and difficult to remove.[8] We imagined that the homocoupling of alkynylborates might be an interesting alternative toward the synthesis of 1,3-diynes.

Comparatively, organoboron reagents are the most intriguing since they are less toxic, stable in air, inexpensive, and environmentally benign. Homocoupling of aryl-, alkenyl-, and alkylboronic acids were well studied.[9] Alkynylborates have long been known to be useful synthetic intermediates.[10] More recently, significant advances have been made in the use of these reagents as coupling partners in a number of palladium mediated carbon–carbon bond forming reactions such as Suzuki type cross-coupling reactions,[11] conjugated addition to enones,[12] allylic additions to allyliccarbonates,[13] and Mannich reaction.[14] We have also reported conventional Suzuki–Miyaura coupling reaction.[15] On the basis of these promising potentialities, our efforts have been made in developing new synthetic methodologies using alkynylborates.[16]

Herein we wish to report an efficient protocol for the synthesis of 1,3-diynes from the alkynylborate salts, which were easily prepared from the known literature procedures.[17] Our initial studies of this process focused on developing an optimum set of reaction conditions for the palladium-catalyzed homocoupling of alkynylborates. The reaction was optimized by using phenylacetyleneborate (**1a**) as a standard substrate as shown in Table 1.

From a series of experiments, it was clear that both the Pd(0) and Pd(II) complexes are effective. We next surveyed solvents such as DMF, THF, THF/water, acetonitrile/water, and 1,4-dioxane. Among the solvents we tested, THF proved to be by far the most effective. The presence of a small quantity of water had no adverse effect on the reaction outcome, so that special drying of the solvent and the reagents was not required. Even though the reaction worked at room temperature albeit in low yield, longer reaction times did not improve the yield significantly (entry 7). We were gratified to learn that the catalytic system of $Pd(OAc)_2$ and bis[(2-diphenylphosphino)phenyl]ether (DPEPhos) in THF at

---

Keywords: Palladium; Catalyst; Homocoupling; Diyne; Borate.

* Corresponding author. Tel.: +82-2-2290-0932; fax: +82-2-2299-0762; e-mail: changho@hanyang.ac.kr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.033

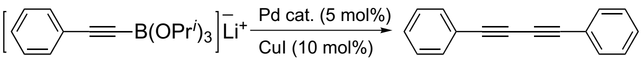
Table 1. Palladium-catalyzed homocoupling of alkynyl triisopropoxy borate (**1a**)

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	$Pd(OAc)_2$/DPEPhos	DMF	120	10	58
2	$Pd(OAc)_2$/DPEPhos	CH_3CN	60	10	63
3	$Pd(OAc)_2$/DPEPhos	CH_3CN/water[a]	60	8	68
4	$Pd(OAc)_2$/DPEPhos	THF/water[a]	60	8	72
5	$Pd(OAc)_2$/DPEPhos	THF	60	6	93
6	$Pd(OAc)_2$/DPEPhos	1,4-Dioxane	80	8	73
7	$Pd(OAc)_2$/DPEPhos	THF	25	6	45
8	$Pd(PPh_3)_4$	THF	60	6	62
9	$PdCl_2/2PPh_3$	THF	60	6	59
10	$Pd(OAc)_2$/TFP	THF	60	6	73
11	$Pd(OAc)_2/2PPh_3$	THF	60	6	71
12[b]	$Pd(OAc)_2$/DPEPhos	THF	60	6	Trace

[a] 10:1 ratio.

[b] Reaction performed in absence of CuI.

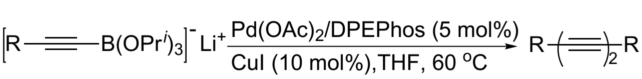
60 °C afforded the corresponding **2a** in 93% yield. It was noteworthy that the present reaction did not require any added base or any other oxidant such as molecular oxygen,[18] $BrCH_2CO_2Et$,[19] allylic acetate,[7] and iodine.[20] We considered Cu(I) salt as a potential co-catalyst because of its ability to catalyze the Sonogoshira reaction. To our great delight, addition of CuI to the $Pd(OAc)_2$/DPEPhos system resulted in exclusive formation of homocoupled product **2a** in 93% yield.[21] In controlled experiment, it was revealed that the presence of CuI is necessary for the smooth transformation (entry 12). When the reaction was carried out under strictly oxygen-free conditions by using freeze–thaw technique, the reaction of **1a** gave the diyne **2a** in 90% yield, implying that the reaction does not require any oxidant. Although this homocoupling reaction was smoothly occurred, mechanistic details were not easily speculated.



1a **2a**

(1)

Having established the viability of the present methodology, we next tested the general applicability as well as the relative reactivity of various alkynylborates. To this end we have prepared a series of alkynylborates from the commercially available triisopropoxyborate with alkynyl lithium, which was in situ prepared from the corresponding terminal alkynes with *n*-BuLi at −78 °C in ether.



1b-o **2b-o**

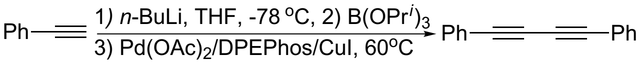
(2)

Most of the substrates were homocoupled under the optimized conditions in good to excellent yields as summarized in Table 2. At first, arylacetylene borates bearing both an electron-deficient group (**1b**) and an electron-rich group (**1c**) worked smoothly under these conditions to afford **2b** and **2c** in 72% and 76% yields, respectively. Alkyl-substituted acetyleneborates such as *tert*-butyl (**1d**) and *n*-butyl (**1e**) gave the even more promising results. While the TMS protected alkynylborate salt **1f** underwent effective homocoupling to afford the product **2f** in 63% yield. Note that these structural motifs are broadly appeared in functional materials as well as in biologically active molecules.[22]

We next employed a series of terminal alkynes bearing an oxy-functionality. The reaction of TBDMS ether **1g** of propargyl alcohol provided the corresponding 1,3-diyne **2g** in good yield. Similarly, THP ether **1h** also worked well without any deprotection. These reactions with TBDMS ethers **1i** and **ij** of 1-butynol and 1-pentynol afforded the corresponding 1,3-diynes **2i** and **2j** in 81% and 78% yields, respectively. Benzyl ether **1k** of 1-hexynol was also effective to furnish the product **2k** in 82% yield.

Finally, the substrates **1l** and **1m** underwent smooth homocoupling to give the products **2l** and **2m** in 68% and 73% yields, respectively. Not surprisingly, two more alkynyl substrates **1n** and **1o** were also effectively homocoupled under these catalytic systems to furnish the products **2n** and **2o** in 62% and 60% yields, respectively. Note that both of these products **2n** and **2o** were obtained as a diastereomeric mixture.

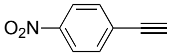
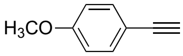
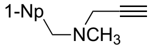
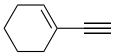
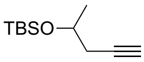
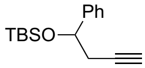
It is clear that the method is tolerant toward a variety of substituents and the yields are very good irrespective of the nature of the substituent. Disappointingly, the use of functionalized alkynes containing an ester, cyano, and a pyridyl substituent failed to prepare corresponding borate salts.



(3)

It was of interest to ascertain whether the two processes could be combined in one pot tandem sequence by temperature control. We treated phenylacetylene with *n*-BuLi in THF at −78 °C, subsequently added triiso-

Table 2. Palladium-catalyzed homocoupling of various alkynylborates

Entry	Substrates	Time (h)	Products	Yield (%)
1	 **1b**	7	**2b**	72
2	 **1c**	6	**2c**	76
3	*tert*-C_4H_9—≡ **1d**	10	**2d**	85
4	*n*-C_4H_9—≡ **1e**	10	**2e**	87
5	Me_3Si—≡ **1f**	4	**2f**	63
6	$TBSOCH_2$—≡ **1g**	6	**2g**	76
7	$THPOCH_2$—≡ **1h**	8	**2h**	64
8	$TBSO(CH_2)_2$—≡ **1i**	6	**2i**	81
9	$TBSO(CH_2)_3$—≡ **1j**	6	**2j**	78
10	$BnO(CH_2)_4$—≡ **1k**	7	**2k**	82
11	 **1l**	10	**2l**	68
12	 **1m**	10	**2m**	73
13	 **1n**	8	**2n**	62
14	 **1o**	10	**2o**	60

propoxyborate, and then treated with a catalytic mixture of $Pd(OAc)_2$, DPEPhos, and CuI in THF by cannula. Upon heating at 60 °C for 6 h, the reaction afforded the corresponding homocouple product **2a** in 82% yield as shown in Eq. 3.

In summary, we have demonstrated a new and highly efficient synthetic method leading to the synthesis of 1,3-diynes under very mild neutral reaction conditions. Use of relatively nontoxic organoborates and commercially cheap Pd(II) catalyst makes this method useful and attractive strategy for the synthesis of conjugated 1,3-diynes. Further studies of this methodology for the synthesis of unsymmetrical 1,3-diynes are currently ongoing in our laboratory and will be published in due course.

Acknowledgements

We wish to acknowledge the financial support of Korea Research Foundation (2001-015-DP0334), Korea., V.R.R. is grateful for a graduate fellowship supported by the BK21 project.

References and notes

1. (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley and Sons: Chichister, 1995; (b) *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 5.
2. (a) Sonogoshira, K.; Thoda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *6*, 4467; (b) Takahashi, K.; Kuroyama, Y.; Sonogoshira, K.; Hagihara, N. *Synthesis* **1980**, 627; (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.
3. (a) Nicolaou, K. C.; Petasis, N. A.; Zipikin, K. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555; (b) Holmes, A. B.; Jennigs-White, C. L. D.; Kendrick, D. A. *J. Chem. Soc., Chem. Commun.* **1983**, 415; (c) Holmes, A. B.; Taber, A. B.; Baker, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3307; (d) Hoye, T. R.; Chansen, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043; (e) Statz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 320.
4. (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632; (b) Fairlamb, I. J. S.; Bauerlein, P. S.; Marrison, L. R.; Dickinson, J. M. *Chem. Commun.* **2003**, *632*; (c) Whittall, J.; Smith, H. E. *Organometalics* **1994**, *13*, 5169; (d) Liao, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2003**, *5*, 909; (e) Fiadnaese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* **2003**, *44*, 9087; (f) Shen, W.; Thomas, A. S. *Org. Lett.* **2000**, *2*, 2857.
5. (a) Kang, S. K.; Kim, T.-H.; Pyun, S.-J. *J. Chem. Soc., Perkin Trans. 1* **1997** 797; (b) Yoshida, H.; Yamaryo, Y.; Oshihata, J.; Kunai, A. *Chem. Commun.* **2003**, 1510.
6. Kang, S. K.; Ryu, H.-C.; Hong, Y.-T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 736.
7. Shirakawa, E.; Yoshiaki, N.; Yasubumi, M.; Tamejiro, H. *J. Organomet. Chem.* **2003**, *670*, 132.
8. For toxicology studies see: (a) Chau, Y. K.; Wong, P. T. S.. In *Some Environmental Aspects of Organo-Arsenic, Lead and Tin*; NBS Special Publication: US, 1981; Vol. 618, p 65;

(b) Sandhu, G. K. *J. Chem. Sci.* **1983**, *9*, 36; (c) Barnes, J. M.; Magos, L. *Organomet. Chem. Rev.* **1968**, *3*(2), 137.

9. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 2457; (b) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213; (c) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178; (d) Oh-e, T.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1990**, 221; (e) Molander, G. A.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 3106; (f) Kabalka, G. W.; Wang, L. *Tetrahedron Lett.* **2002**, *43*, 3067; (g) Parish, J. P.; Jung, Y. C.; Floyd, R. J.; Jung, K. W. *Tetrahedron Lett.* **2002**, *43*, 7899; (h) Yoshida, H.; Yamaryo, Y.; Oshihata, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541.
10. (a) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419; (b) Colberg, J. C.; Rane, A.; Vaquer, J.; Soderquist, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 6065; (c) Soderquist, J. A.; Matos, K.; Rane, J.; Ramos *Tetrahedron Lett.* **1995**, *36*, 2401; (d) Furstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 1165; (e) Furstner, A.; Seidel, G. *Synlett* **1997**, 161.
11. (a) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416; (b) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393; (c) Molander, G. A.; Reviro, M. R. *Org. Lett.* **2002**, *4*, 107; (d) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867; (e) Batey, A. B.; Quatch, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099; (f) Fang, G.-H.; Zeng-Jun, Y.; Deng, M.-Z. *Org. Lett.* **2004**, *6*, 357; (g) Zou, G.; Flack, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817.
12. (a) Chong, M. J.; Shen, L.; Nicholas, J. T. *J. Am. Chem. Soc.* **2000**, *122*, 1822; (b) Battey, A. R.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683; (c) Brown, C. D.; Chong, J. M.; Shen, L. *Tetrahedron* **1999**, *55*, 14233.
13. (a) Chen, H.; Deng, M.-H. *J. Organomet. Chem.* **2000**, *603*, 189; (b) Kobayashi, Y.; Mizojiri, R.; Ikeda, E. *J. Org. Chem.* **1996**, *61*, 5391.
14. Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2004**, *45*, 729.
15. Oh, C. H.; Jung, S. H. *Tetrahedron Lett.* **2000**, *41*, 8513.
16. (a) Oh, C. H.; Jung, H. H.; Kim, K. S. *Angew Chem., Int. Ed.* **2003**, *42*, 805; (b) Oh, C. H.; Ahn, T. W.; Reddy, V. R. *Chem. Commun.* **2003**, 2622; (c) Kim, N.; Oh, C. H.; Kim, K. S.; Gupta, A. K. *Chem. Commun.* **2004**, 618; (d) Oh, C. H.; Ryu, J. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 1563.
17. (a) Brown, H. C.; Cole, T. E. *Organometalics* **1983**, *2*, 1316; (b) Brown, H. C.; Bhatt, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631.
18. (a) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320; (b) Valenti, E.; Pericas, M. A.; Serratosa, F. *J. Am. Chem. Soc.* **1990**, *112*, 7405; (c) Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Gayatri, K. U.; Prasad, A. R. *Tetrahedron Lett.* **2003**, *44*, 6493.
19. Lei, A.; Srivastava, M.; Zang, X. *J. Org. Chem.* **2002**, *67*, 1969.
20. (a) Pelter, A.; Smith, K.; Tabata, M. *J. Chem. Soc., Chem. Commun.* **1975**, 857; (b) Damle, V. S.; Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2003**, *68*, 7085.
21. Representative experimental procedure: To a mixture of lithium alkynyl triisopropoxy borate **1a** (1 mmol), Pd(OAc)$_2$ (0.05 mmol), DPEPhos (0.05 mol %), and CuI (0.10 mmol %), THF (2.0 mL) was added under argon atmosphere and the mixture was stirred at 60 °C. After heating for the time specified, the reaction mixture was allowed to cool to room temperature. The product was extracted into diethyl ether (3×10 mL), the solvent was removed in vacuo to yield the crude product as a brown oil that was purified by column chromatography on silica gel. All products were characterized by ^{1}H-, ^{13}C NMR, FT-IR, and HRMS.
22. (a) Valenti, E.; Pericas, M. A.; Serratosa, F. *J. Am. Chem. Soc.* **1990**, *112*, 7405; (b) Kitamura, T.; Lee, C. H.; Taniguchi, Y.; Fujiwara, Y. *J. Am. Chem. Soc.* **1997**, *119*, 619.