Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 49 (2008) 2366–2370

Tetrahedron Letters

Copper salt-catalyzed homo-coupling reaction of potassium alkynyltrifluoroborates: a simple and efficient synthesis of symmetrical 1,3-diynes

Marcio W. Paixão[a,*], Minéia Weber[b], Antonio L. Braga[d], Juliano B. de Azeredo[d], Anna M. Deobald[d], Hélio A. Stefani[a,b,c,*]

[a] *Instituto de Química, Universidade de São Paulo, SP, Brazil*
[b] *Departamento de Biofísica, Universidade Federal de São Paulo, São Paulo, SP, Brazil*
[c] *Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo—SP, Brazil*
[d] *Departamento de Química, Universidade Federal de Santa Maria, Santa Maria, RS, Brazil*

Received 18 December 2007; revised 29 January 2008; accepted 14 February 2008
Available online 19 February 2008

Abstract

The copper-catalyzed dimerization of alkynyltrifluoroborates proceeds readily with good yields. The homo-coupling reaction can be effected in DMSO, in the open air, using $Cu(OAc)_2$ as catalyst in the absence of any other additives. A variety of functional groups are tolerated.

1. Introduction

Diyne compounds are of great importance as versatile building blocks[1] in organic synthesis. In this context, 1,3-diynes have been prominently used as equivalents of various functional groups in organic synthesis[2] as well as valuable intermediates for natural products[3] and pharmaceuticals, particularly antifungal agents.[4] Specially noteworthy is that 1,3-diynes have been recently recognized as a core functional group in organic molecular materials such as molecular wires and molecular architecture on the nanometer scale.[5]

This type of compound can be synthesized by the traditional Glaser oxidative dimerization of terminal acetylenes[6] and can also be formed by Pd(0)–Cu(I) catalyzed self-coupling of terminal alkynes in the presence of chloroacetone,[7] ethyl bromoacetate,[8] allyl bromide,[9] and iodine.[10] The dimerization of terminal alkynyl halides with terminal alkynes under palladium-catalyzed conditions is another route to diynes.[11] The most common catalytic system is a combination of Pd catalyst with an amine.[12] However, both are expensive and amines often have characteristic foul smell and pungent flavors.

From the view of economic and environmental points, development of cheaper metals as catalysts in place of Pd is an attractive route, in spite of the difficult recovery as well as recycling of the Pd catalyst.[13] Although copper has been applied as catalyst in many cross-coupling transformations, little attention has been paid to the use of copper as catalyst for homo-coupling reaction without any other additives.[14]

Diverse organoboron components have been utilized effectively for homo-coupling reactions. For example, lithium alkylnyltriisopropoxyborates are generally efficient partners, in this case, the procedure requires the use of a catalytic amount of a homogenous palladium catalyst, copper salt, and phosphine ligand.[15] Boronic esters derived from pinacol are also widely used in homo-coupling reactions. There are several potential problems with these

---

[*] Corresponding authors. Tel.: +55 11 3091 3864; fax: +55 11 3815 4418 (H.A.S.).
E-mail addresses: marelloweber@gmail.com (M. W. Paixão), hstefani@usp.br (H. A. Stefani).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.083

derivatives. Boronic esters or diethanolamine adducts are often utilized as a means to purify these organoboron species, but some of these esters are hydrolytically stable and/or difficult to handle. Furthermore, the diols utilized to create these derivatives (e.g., catechol, pinacol, or the diethanolamine) add considerable expense to the overall process and, additionally, must be separated from the desired product. A lack of atom economy also exists for the boronic esters in coupling processes, wherein again the diols comprising these reagents must be separated from the final product and disposed. Finally, superstoichiometric amounts of copper must often be used for efficient coupling of alkylnylboronates.[16]

By contrast, potassium organotrifluoroborates have been shown to overcome this particular limitation. These salts are unique organoboron compounds, notable for their stability to moisture and air.[17] They are powders or crystalline solid that are easy to access and handle, and these properties have made them attractive synthetic intermediates.[18]

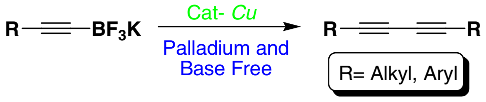
Herein, we describe our initial efforts to develop a convenient and practical access to symmetrical 1,3-diynes via homo-coupling of potassium alkynyltrifluoroborates mediated by a catalytic amount of copper salts in the absence of any other additive (Scheme 1).

First, we chose potassium phenylethynyltrifluoroborates, a very active substrate, to establish the viability of the method. We examined the role of solvents, copper sources, and loading of catalyst to elucidate the general reaction conditions with the goal of high yields for a wide survey of substrates. We hoped to achieve good reactivity with this active substrate and then apply these conditions to more difficult substrates.

A series of solvents were first examined for the homo-coupling of phenylethynyltrifluoroborates in the presence of $Cu(OAc)_2$ (10 mol %) at 60 °C for 6 h under air atmosphere (Table 1).

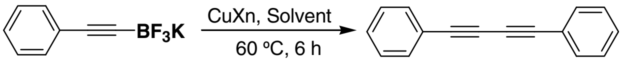
The desired 1,3-diyne was generated in low yields in CH_2Cl_2, and THF (Table 1, entries 2 and 3), while moderate to excellent yields were achieved in polar aprotic solvents such as DMF, DME, and DMSO (entries 1 vs 4 and 5). It is noteworthy that the copper-catalyzed homo-coupling reaction of potassium phenylethynyltrifluoroborates proceeded with a high efficiency in DMSO, which was the best solvent for the reaction under palladium- and base-free conditions (entry 1).

The next step was the determination of the best copper catalyst, the copper(I) and (II) species were used in the coupling reactions and the best result was achieved with $Cu(OAc)_2$ (compare entries 1 vs 6–10). The catalyst loadings were also analyzed. It was observed that using 5 and 2.5 mol % of the catalyst, the desired 1,4-diphenylbuta-1,3-diyne was obtained with 65% and 10% of yield, respectively (entries 11 and 12).



Scheme 1. Preparation of symmetrical 1,3-diynes.

Table 1
Copper-catalyzed homo-coupling of potassium phenylethynyltrifluoroborates using various solvents



Entry	CuX_n (mol %)	Solvent	Yield[a] (%)
1	$Cu(OAc)_2$ (10)	DMSO	97
2	$Cu(OAc)_2$ (10)	THF	4
3	$Cu(OAc)_2$ (10)	CH_2Cl_2	2
4	$Cu(OAc)_2$ (10)	DMF	47
5	$Cu(OAc)_2$ (10)	DME	25
6	CuCl (10)	DMSO	89
7	CuI (10)	DMSO	25
8	CuCN (10)	DMSO	4
9	CuOTf (10)	DMSO	8
10	$CuCl_2$ (10)	DMSO	34
11	$Cu(OAc)_2$ (5)	DMSO	65
12	$Cu(OAc)_2$ (2.5)	DMSO	10

[a] Yields related to pure isolated products characterized by spectroscopic data.

The mild reaction conditions, its speed and the excellent yields obtained encouraged us to examine the scope and generality of the present method. Various potassium alkynyltrifluoroborates[19] were then examined for the homo-coupling reaction with the $Cu(OAc)_2$/DMSO system[20] and the results are summarized in Table 2.

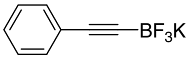
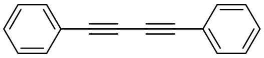
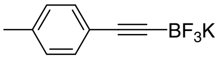
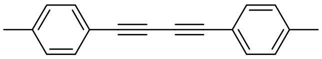
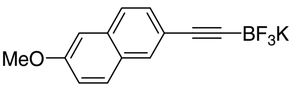
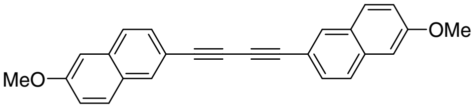
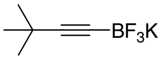
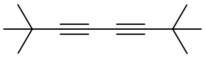
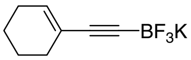
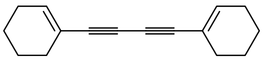
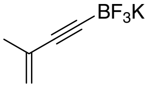
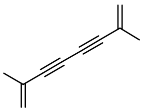
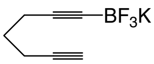
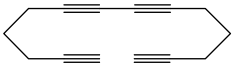
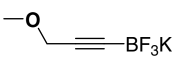
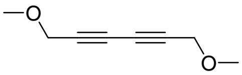
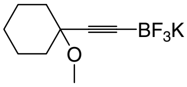
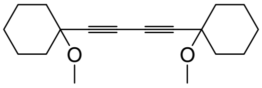
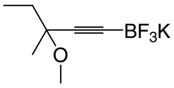
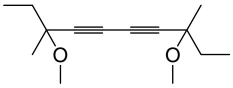
At first, aromatic alkynyltrifluoroborate bearing an electron-rich group reacted smoothly under these conditions to afford the desired product in 84% yield (Table 2, entry 2). Interestingly, naphthyl alkynyltrifluoroborate can also undergo the self-coupling reaction with good yield (82%, entry 3).

We then examined the application of the present $Cu(OAc)_2$/DMSO system to the coupling reaction of various aliphatic alkynyltrifluoroborates (entries 4–9). When the alkynyltrifluoroborate derived from 1-hexyne was employed as the substrate, the corresponding 1,3-diyne was obtained in an excellent yield (86%). The substrate derived from 1-octyne, underwent smooth homo-coupling to give the product in 88% yield (entry 5). The reactivity of the *tert*-butyl substituted alkynyltrifluoroborates was also investigated; and the homo-coupling product was obtained in 66% of yield (entry 6). Not surprisingly, four more alkynyl substrates were also effectively homocoupled under this catalytic system to furnish the desired products in 87%, 88%, and 42%, respectively (entries 6–8).

Finally, we next employed a series of alkynyltrifluoroborates bearing an oxy-functionality (entries 10–12). The reaction of methyl ether of propargyl alkynyltrifluoroborates provide the corresponding 1,3-diyne in 58% isolated yield (entry 10). Sterically hindered methyl ether alkynyltrifluoroborates were also effectively applicable to

Table 2
Preparation of symmetrical 1,3-diynes from potassium alkynyltrifluoroborates using $Cu(OAc)_2$/DMSO system

$$R{-}C{\equiv}C{-}BF_3K \xrightarrow[\text{DMSO, 60 °C, 6 h}]{Cu(OAc)_2 \text{ (10 mol \%)}} R{-}C{\equiv}C{-}C{\equiv}C{-}R$$

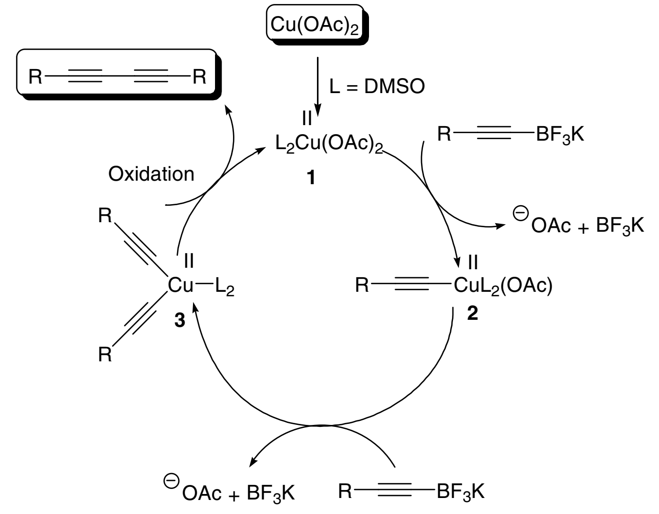
Entry	Substrate	Product	Yield[a] (%)
1			97
2			84
3			82
4	n-C_4H_9—≡—BF_3K	n-C_4H_9—≡—≡—n-C_4H_9	86
5	n-C_6H_{13}—≡—BF_3K	n-C_6H_{13}—≡—≡—n-C_6H_{13}	88
6			66
7			87
8			88
9			42
10			58
11			60
12			28

[a] Yields related to pure isolated products characterized by spectroscopic data.

the homo-coupling to give the corresponding 1,3-diynes (entries 11 and 12).

As outlined in Scheme 2, we have formulated a proposed mechanism for the copper-catalyzed homo-coupling of alkynyltrifluoroborates. First, the alkynyltrifluoroborates reacted with copper(II) acetate **1** to form alkynylcopper(II) **2** in the presence of DMSO as a solvent. Reductive elimination of the dialkynylcopper(II) intermediate **3** could undergo to form the desired diyne and Cu(0). Finally, Cu(0) was oxidated by O_2 and DMSO to generate the active Cu(II) species **1** leading to a new catalytic cycle.[21]

In summary, copper-catalyzed conditions in the absence of palladium and base have been found to be suitable for the homo-coupling of potassium alkynyltrifluoroborate salts. The reaction proved to be tolerant to a variety of functional groups. It can be carried out in DMSO in the air, with 10% of catalyst loading in relatively short reaction times. The high yields, in addition to the environmental characteristics of the boron byproducts, allow simple workup techniques to be applied to obtain products with greater than 97% purity. These features, combined with the shelf stability of the alkynyltrifluoroborate salts, make this technique environmentally sound, economical, and very attractive for use in industrial processes and combinatorial chemistry.



Scheme 2. Possible mechanism for the copper-catalyzed homo-coupling reaction.

Acknowledgments

The authors gratefully acknowledge CNPq, CAPES (fellowship to M.W.), and FAPESP (Grant 07/59404-2 and fellowship to M.W.P.) for a financial support.

References and notes

1. (a) Hunstman, V. D. In *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, S., Ed.; Wiley-Interscience: London, 1978; p 553; (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.
2. For general reviews on coupling reactions between an sp carbon center, see: (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 3, pp 551–561; (b) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320; (c) Rossi, R.; Carpita, A.; Bigelli, C. *Tetrahedron Lett.* **1985**, *26*, 523; (d) Jones, G. E.; Kendrick, D. A.; Holmes, A. B. *Org. Synth.* **1987**, *65*, 52; (e) Valenti, E.; Pericas, M. A.; Serratosa, F. *J. Am. Chem. Soc.* **1990**, *112*, 7405; (f) Liu, G.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 4371; (g) Kitamura, T.; Lee, C. H.; Taniguchi, Y.; Fujiwara, Y. *J. Am. Chem. Soc.* **1997**, *119*, 619; (h) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.
3. (a) Holmes, A. B.; Jennings-White, C. L. D.; Kendrick, D. A. *J. Chem. Soc., Chem. Commun.* **1983**, 415; (b) Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 3548; (c) Crombie, L.; Hobbs, A. J. W.; Horsham, M. A. *Tetrahedron Lett.* **1987**, *28*, 4875; (d) Holmes, A. B.; Tabor, A. B.; Baker, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3307; (e) Hoye, T. R.; Chanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043; (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034.
4. (a) Stuüts, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 320; (b) Shun, A. L. K. S.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034.
5. (a) Fouquey, C.; Lehn, J.-M.; Malthete, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1424; (b) Diederich, F.; Rubin, Y.; Knobler, C. B.; Whetten, R. L.; Schriver, K. E.; Houk, K. N.; Li, Y. *Science* **1989**, *245*, 1088; (c) Kanis, D. R.; Ratner, M. A.; Marks, T. J. *Chem. Rev.* **1994**, *94*, 195; (d) Xu, Z.; Kaha, M.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4537.
6. (a) Has, A. S. *J. Org. Chem.* **1962**, *27*, 3320; (b) Mkryan, M. G.; Papazyan, N. A.; Voskayan, E. S.; Khachaturyan, I. V. *Arm. Khim. Zh.* **1966**, *19*, 938; *Chem. Abstr.* **1966**, *67*, 43373z; (c) Valenti, E.; Pericas, M. A.; Serratosa, F. *J. Am. Chem. Soc.* **1990**, *112*, 7405; (d) Maruyama, K.; Tsukube, H.; Araki, T. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 749; (e) Liao, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2003**, *5*, 909.
7. Rossi, R.; Carpita, A.; Bigelli, C. *Tetrahedron Lett.* **1985**, *26*, 523.
8. Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 196.
9. Vlasa, M.; Ciocan-Tarta, I.; Margineanu, F.; Oprean, I. *Tetrahedron* **1996**, *52*, 1337.
10. Liu, Q.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 4371.
11. (a) Kurita, T.; Abe, M.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Synlett* **2007**, 2521; (b) Shi, M.; Quian, H.-X. *Appl. Organometal. Chem.* **2006**, *20*, 771; (c) Yan, J.; Wu, J.; Jin, H. *J. Organometal. Chem.* **2007**, *692*, 3636.
12. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
13. For papers on the other coupling reactions catalyzed by a catalytic amount of copper see: (a) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716; (b) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315; (c) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *Green Chem.* **2004**, *6*, 215; (d) Ma, D.; Liu, F. *Chem. Commun.* **2004**, 1934; (e) Wang, Y. F.; Deng, W.; Liu, L.; Guo, Q. X. *Chin. Chem. Lett.* **2005**, *16*, 1197; *Chem. Abstr.* **2005**, *144*, 22662; (f) Saejueng, P.; Bates, C. G.; Venkataraman, D. *Synthesis* **2005**, 1706; (g) Xie, Y.-X.; Deng, C.-L.; Pi, S.-F.; Li, J.-H.; Yin, D.-L. *Chin. J. Chem.* **2006**, *24*, 1290; (h) Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* **1997**, *62*, 4208; (i) Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 1109; (j) Mohapatra, S.; Bandyopadhyay, A.; Barma, D. K.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4759; (k) Kang, S.-K.; Yamaguchi, T.; Kim, T.-H.; Ho, P.-S. *J. Org. Chem.* **1996**, *61*, 9082; (l) Li, J.-H.; Tang, B.- X.; Tao, L.-M.; Liang, Y.; Zhang, M.-B. *J. Org. Chem.* **2006**, *71*, 7488.
14. (a) Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007**, *72*, 2053; (b) Li, J.-H.; Li, J.-L.; Xie, Y.-X. *Synthesis* **2007**, *7*, 984; (c) Zhu, B. C.; Jiang, X. Z. *Appl. Organometal. Chem.* **2007**, *21*, 345.
15. Oh, C. H.; Reddy, V. R. *Tetrahedron Lett.* **2004**, *45*, 5221.
16. Nishihara, Y.; Okamoto, M.; Inoue, Y.; Miyazaki, M.; Miyasaka, M.; Takagi, M. *Tetrahedron Lett.* **2005**, *46*, 8661.
17. For the synthesis of organotrifluoroborates, see: (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020; (b) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460; (c) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416.
18. For reviews of organotrifluoroborate salts, see: (a) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49; (b) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 4313; (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275; (d) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623.
19. *General procedure for the preparation of potassium alkynyltrifluoroborate salts*. A solution of alkyne (10 mmol, 1 equiv) in 20 mL of dry THF was cooled to −78 °C under argon. *n*-BuLi (6.25 mL, 1.6 M in hexane, 10 mmol, 1 equiv) was added dropwise, and the solution was stirred for 1 h at this temperature. Trimethylborate (1.56 g, 15 mmol, 1.5 equiv) was then added dropwise at −78 °C. The solution was stirred at this temperature for 1.5 h after which it was allowed to warm to −20 °C for 1.5 h. A saturated aqueous solution of KHF$_2$ (4.7 g, 60 mmol, 6.0 equiv) was added to the vigorously stirred solution. The resulting mixture was allowed to stir for 1 h at −20 °C after which it was allowed to warm to room temperature for 1 h. The solvent was removed under reduced pressure, and the resulting white solid was dried under high vacuum for 2 h to remove all water. The solid was then washed with acetone and with hot acetone. The resulting organic solution was filtered, and the solvent was removed to afford a white solid. This solid was then dissolved in hot acetone and precipitated with diethyl ether, after which the solution was cooled to −20 °C to complete precipitation of the solid.

20. *General procedure for the alkynyltrifluoroborates dimerization*. To a mixture of alkynyltrifluoroborates (0.5 mmol) and $Cu(OAc)_2$ (10 mol %), DMSO (3 mL) was added. The mixture was stirred at 60 °C for 6 h. After this time, the mixture was filtered and the solvents evaporated. The crude product was purified by silica gel column chromatography, eluting with hexane to give the corresponding pure 1,3-diyne.
21. (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337; (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.