Tetrahedron Letters 50 (2009) 4324–4327

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed oxidative homocoupling of potassium alkenyltrifluoroborates: synthesis of symmetrical 1,3-dienes

Minéia Weber[a], Fateh V. Singh[b], Adriano S. Vieira[b], Hélio A. Stefani[a,b,*], Marcio W. Paixão[c,*]

[a] Universidade Federal de São Paulo, Departamento de Biofisica, São Paulo—SP, Brazil
[b] Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo—SP, Brazil
[c] Instituto de Química, Universidade de São Paulo—SP, Brazil

ARTICLE INFO

Article history:
Received 16 March 2009
Revised 27 April 2009
Accepted 30 April 2009
Available online 5 May 2009

Keywords:
Homocoupling reaction
1,3-Dienes
Organotrifluoroborates
Alkenyltrifluoroborates

ABSTRACT

Herein, we describe a convenient method for the synthesis of symmetrical 1,3-dienes employing an oxidative palladium-catalyzed homocoupling of potassium alkenyltrifluoroborates providing products in good yields relative to existing methodologies. This is the first report of a cross-dimerization of potassium alkenyltrifluoroborates.

Transition metal-catalyzed cross-coupling reactions have emerged as powerful and general methods for the synthesis of organic compounds.[1] C–C bond-formation processes, which are typically mediated by nickel, palladium, iron, or copper catalysis, are now ubiquitous in both academia and industry.[2]

The stereo and regio-defined synthesis of conjugated dienes has been a long-standing challenge in organic synthesis. Success in this area is still warranted as this structural motif is prevalent in biologically active compounds, as well as in conducting polymers and liquid crystalline materials.[3]

A number of methods for the preparation of conjugated dienes and polyenes have been previously developed employing a number of varied organometallic reagents. However, apart from the formation of the major cross-coupling product, a minor byproduct resulting from the palladium-catalyzed homocoupling reaction is often observed.[4] Recently, the palladium-catalyzed homocoupling of an alkenyl-metal was developed as the primary pathway when performed in the presence of a chemical oxidant, either oxygen or air.[5]

Among the organometallic reagents employed in cross-coupling reactions, organoboron species (in particular in the Suzuki–Miyaura reaction) offer advantages over other partners such as Grignard reagents, organozinc reagents, and organostannanes.[6] They are readily prepared and in many cases they are commercially available. Additionally, the coupling reaction conditions are often mild and the resulting inorganic byproducts are environmentally benign and are easily removed by simple workup procedures.

The most commonly used organoboron species include boronic acids and boronate esters. Unfortunately, these functionalities bear certain drawbacks, including high price, and sensitivity to air and moisture. As such, organoboronic acid and ester derivatives have been replaced by potassium organotrifluoroborate salts, which are crystalline solids, stable under air and moisture, and readily prepared from inexpensive materials. They are also considerably more nucleophilic than their predecessors.[7]

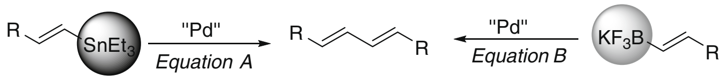
As a part of our research efforts with potassium organotrifluoroborates as a key reagent in cross- or homocoupling reactions,[8] we recently reported the use of potassium alkynyltrifluoroborates for the simple and efficient synthesis of symmetrical 1,3-diynes.[9] To this end, we propose herein a simple analogous experimental procedure employing potassium alkenyltrifluoroborates.[10] These reagents are easy to handle, less toxic than alkenylstannanes, and active enough to promote direct oxidative homocoupling (Scheme 1, Eq. A vs B). Our study resulted in the synthesis of conjugated 1,3-diene derivatives under mild and neutral conditions.

We initially focused our attention on optimization of reaction conditions for the Suzuki–Miyaura homocoupling reaction of potassium alkenyltrifluoroborates. We used a variety of catalysts, co-oxidants, and solvents. Model reaction conditions were explored using stereodefined reagents to study the stereochemistry of the formed 1,3-diene.

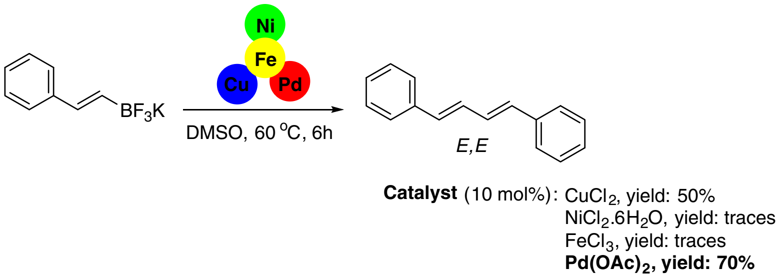
---

* Corresponding authors. Tel.: +55 11 3091 3654; fax: +55 11 3 815 4418 (H.A.S.).
E-mail address: hstefani@usp.br (H.A. Stefani).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.04.127



Scheme 1.



Scheme 2.

A series of catalysts (e.g., Ni, Fe, Cu, and Pd) were first examined for the homocoupling of *trans*-styryltrifluoroborate using DMSO as solvent at 70 °C for 7 h (Scheme 2).

Unfortunately, the methodology that had previously been described for achieving the homocoupling of potassium alkynyltrifluoroborates[9] was not useful for alkenylboron species. Suboptimal results were also obtained with 10 mol % $NiCl_2 \cdot 6H_2O$ or $FeCl_3$. However, $Pd(OAc)_2$ proved to be efficient, providing the *E,E*-1,3-dienes in 70% yield. Other Pd precursors including $Pd(Acac)_2$, $PdCl_2(PhCN)$, and $Pd(PPh_3)_4$ afforded significantly moderate results (Table 1, entries 1–3). The yield could be further improved by employing 15 mol % of $Pd(OAc)_2$ in the presence of Ag_2O as a co-oxidant (78%, entry 4).

Upon identification of an efficient catalyst, we studied the influence of solvent. The desired 1,3-diene was generated in moderate yield in polar aprotic and protic solvents such as DMF, CH_3CN, and MeOH (entries 5-7 vs 10). THF provided a significantly lower yield (entry 9). As a result of the solvent screening, subsequent studies were performed in DMSO. We also examined the participation of other co-oxidants. For example, when (diacetoxyiodo)benzene was employed, the desired homocoupling product was obtained in 63% yield (entry 11).

The mild reaction conditions, the high reaction rate, and the reasonable yields obtained encouraged us to examine the scope and generality of the present method. Various, potassium alkenyltrifluoroborates[10] were than examined for homocoupling with the $Pd(OAc)_2/Ag_2O$ system,[11] and the results are summarized in Table 2.

Deactivated aromatic alkenyltrifluoroborates bearing electron-donating substituents such as methoxy or methyl, reacted smoothly under these conditions to afford the desired products in moderate yield (Table 2, entries 2 and 3). Interestingly, activated alkenylborates also undergo the self-coupling reaction with the same range of yield (entries 3 vs 4). In all cases (entries 1–4), the (*E,E*)-dienes were obtained as pure isomers as determined by ^1H NMR.

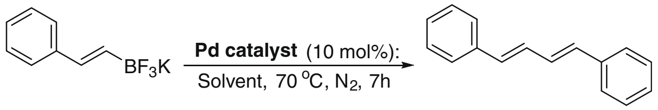
We next examined the application of this palladium system to the coupling reaction of aliphatic alkenyltrifluoroborates (entries 5 and 6). When the alkenyltrifluoroborate derived from but-3-ynylbenzene was employed, the corresponding 1,3-dienes were obtained in suitable yield (56%). The substrate derived from 1-heptyne provided the homocoupling product in 42% yield (entry 6). Finally, the presence of α-substitution in the organoboron partner (entry 7) was also studied. Interestingly, potassium isopropenyltrifluorate proved to be an ineffective reagent for the homocoupling reaction.

Next, we turned our attention to competition experiments to determine if the reactivity trends of the alkenyltrifluoroborates were dependent upon the reaction conditions. For this reaction type, we employed capillary gas chromatographic analysis of the reaction mixture as the analytical tool for accurate determination of product ratios. Competition experiments were conducted with different aromatic alkenyltrifluoroborates[12] in the presence of 15 mol % of $Pd(OAc)_2$ and Ag_2O using DMSO as solvent (Table 3).

After complete consumption of starting materials (observed by TLC), the product ratios were determined quantitatively by GC–MS analysis. The self-coupling product ratios obtained with a mixture of *p*-tolyl alkenyltrifluoroborate and *p*-bromophenyl alkenyltrifluoroborate were 24% and 16%, respectively; however, the cross-coupling product was obtained in 60% (Table 3, entry 1). By contrast, *p*-anisole alkenyltrifluoroborate was significantly less reactive than the *p*-bromophenyl alkenyltrifluoroborate. The desired homocoupling products were obtained in a 2:1 ratio in preference of the activated alkenylborate. Again, the cross-coupling product was obtained as the major product (entry 2).

In conclusion, we have demonstrated a convenient method for the synthesis of symmetrical 1,3-dienes. Products are formed in good yields with pertinent modifications over existing methodologies. Additionally, this method represents the first report of a cross-dimerization of potassium alkenyltrifluoroborates. Further extensions of this methodology will be reported in due course.

Table 1
Effect of reaction parameters



Entry	Pd source	Solvent	Yield (%)[a]
1	$Pd(Acac)_2$	DMSO	54
2	$PdCl_2(PhCN)$	DMSO	47
3	$Pd(PPh_3)_4$	DMSO	43
4[b]	$Pd(OAc)_2$	DMSO	78
5[b]	$Pd(OAc)_2$	DME	66
6[b]	$Pd(OAc)_2$	DMF	72
7[b]	$Pd(OAc)_2$	CH_3CN	71
8[b]	$Pd(OAc)_2$	1,4-Dioxane	49
9[b]	$Pd(OAc)_2$	THF	18
10[b]	$Pd(OAc)_2$	MeOH	51
11[c]	$Pd(OAc)_2$	DMSO	63

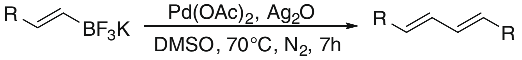
[a] Yields describe the isolation of pure products characterized by spectroscopic data.

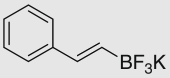
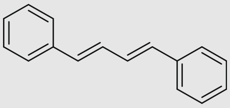
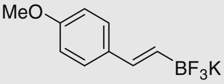
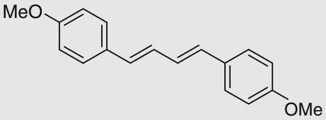
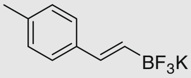
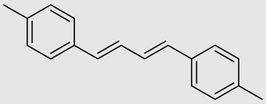
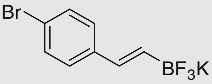
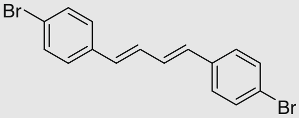
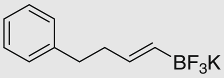
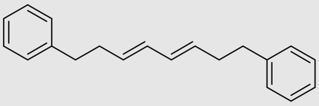
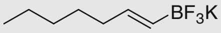
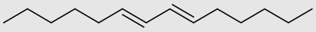
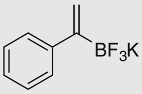
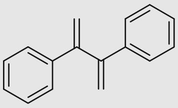
[b] The reactions were conducted using 15 mol % of catalyst in the presence of 3 equiv of Ag_2O.

[c] The reaction was carried out using 15 mol % catalyst and 1 equiv (diacetoxyiodo)benzene.

Table 2

Synthesis of symmetric 1,3-dienes from potassium alkenyltrifluoroborates using the Pd(OAc)$_2$/Ag$_2$O system



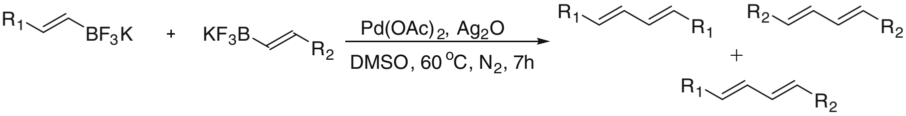
Entry	Substrate	Product	Yield (%)[a]
1			78
2			42
3			65
4			62
5			56[b]
6			42[b]
7			n.r.

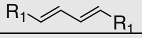
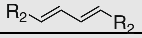
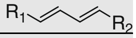
[a] Yields describe the isolation of pure products characterized by spectroscopic data.

[b] Mixture of isomers (entry 5, 30:70; entry 6, 88:8:4).

Table 3

Competition experiments: effect of the aromatic substituents



Entry	R_1	R_2	Product ratios[a] (%)		
					
1	MeC_6H_4	BrC_6H_4	24	16	60
2	$MeOC_6H_4$	BrC_6H_4	19	36	45
3	Ph	MeC_6H_4	28	14	58
4	Ph	BrC_6H_4	38	32	30

[a] Product ratios were determined by GC–MS.

Acknowledgments

The authors gratefully acknowledge CNPq (300613/2007-5), CAPES (fellowship to M.W.), and FAPESP (Grant 07/59404-2) for financial support.

References and notes

1. (a) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834; (b) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840–871.
2. (a)For an indispensable book on cross-coupling, see: *Metal-Catalyzed Cross Coupling Reactions*; de Meijere, A., Diederich, F., Eds., 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004; For a Review in Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis see: (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
3. Negishi, E.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474.
4. Kotora, M.; Takahashi, T. *Handbook of Organopalladium Chemistry for Organic Synthesis* 2002; Vol. 1, p 973.
5. Nishibayashi, Y.; Cho, C. S.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **1996**, *526*, 335.
6. (a) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: Berlin, 1995; (b) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic: London, 1988; (c) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439.
7. For reviews of organotrifluoroborate salts, see: (a) Darses, S.; Genêt, J. P. *Eur. J. Org. Chem.* **2003**, 4313; (b) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49; (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; (e) Darses, S.; Genêt, J. P. *Chem. Rev.* **2008**, *108*, 288.

8. (a) Cella, R.; Venturoso, R. C.; Stefani, H. A. *Tetrahedron Lett.* **2008**, *49*, 16; (b) Bellomo, A.; Gonzalez, D.; Stefani, H. A. *J. Organomet. Chem.* **2008**, *693*, 1136; (c) Vieira, A. S.; Guadagnin, R. C.; Fiorante, P. F.; Ferreira, F. P.; Stefani, H. A. *Tetrahedron* **2008**, *64*, 3306; (d) Vieira, A. S.; Fiorante, P. F.; Zukerman-Schpector, J.; Alves, D.; Botesselle, G. V.; Stefani, H. A. *Tetrahedron* **2008**, *64*, 7234; (e) Guadagnin, R. C.; Suganuma, C.; Vieira, A. S.; Cella, R.; Stefani, H. A. *Tetrahedron Lett.* **2008**, *49*, 4713; (f) Singh, F. V.; Weber, M.; Guadagnin, R. C.; Stefani, H. A. *Synlett* **2008**, 1889; (g) Botteselle, G. V.; Hough, T. L. S.; Venturoso, R. C.; Cella, R.; Vieira, A. S.; Stefani, H. A. *Aust. J. Chem.* **2008**, *61*, 870; (h) Vieira, A. S.; Fiorante, P. F.; Hough, T. L. S.; Ferreira, F. P.; Lüdtke, D. S.; Stefani, H. A. *Org. Lett.* **2008**, *10*, 5215; (i) Singh, F. V.; Stefani, H. A. *Synlett* **2008**, 3221.
9. Paixão, M. W.; Weber, M.; Stefani, H. A.; Braga, A. L.; Azeredo, J. B.; Deobald, A. M. *Tetrahedron Lett.* **2008**, *49*, 2366.
10. *General procedure for potassium alkenyltrifluoroborate synthesis*: In a dried two-necked 50-mL flask with a nitrogen atmosphere was added dropwise 4-methyl phenylacetylene (20 mmol, 2.65 mL) at 0 °C. Catecholborane (20 mmol, 2.15 mL) was then added dropwise at the same temperature. The ice bath was removed, and the resulting mixture was heated and stirred for 4 h at 75 °C, after which it was allowed to cool to room temperature. Next, a saturated aqueous solution of potassium hydrogen difluoride (80 mmol, 6.24 g) was added to the vigorously stirred solution. After 5 h, a white precipitate was formed, the solvent was removed under reduced pressure, and the resulting white solid was washed with acetone (100 mL) and with hot acetone. The resulting organic solution was filtered, and the solvent was removed to afford a fluffy white solid. This solid was then dissolved in hot acetone and precipitated with cold diethyl ether (40 mL), after which the solution was cooled to −20 °C to complete the precipitation of the solid. The product was collected as a white crystalline solid (62%). ^{1}H NMR: (DMSO-d_6, 300 MHz): δ 7.18 (d, J = 7.6 Hz, 2H); 7.03 (d, J = 7.6 Hz, 2H); 6.42 (d, J = 18.2 Hz, 1H); 6.09 (d, J = 18.2 Hz, 1H); 2.23 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 138.05, 135.21, 133.37, 129.30, 125.75, 21.16. ^{11}B NMR (DMSO-d_6, 96 MHz): δ 3.61; ^{19}F NMR (DMSO-d_6, 282 MHz): δ −137.7.
11. General procedure for all homocoupling reactions (Table 2, entry 2): A 50-mL flask under a nitrogen atmosphere was charged with potassium methyl styryltrifluoroborate (0.5 mmol, 0.112 g), Pd(OAc)$_2$ (15 mol %, 16.50 mg), Ag$_2$O (3 equiv, 34.76 mg), and DMSO (3 mL). The reaction mixture was heated at 70 °C for 7 h and the reaction was followed by TLC. After completion, the reaction mixture was allowed to reach rt and then NH$_4$Cl (30 mL) was added, and the organic phase was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, dried (MgSO$_4$), and the solvent was removed under vacuum to provide a viscous yellow oil. The oil was purified by column chromatography using a mixture of hexane/ethyl acetate (96:4) as the eluent to afford the solid products (see Table 2). Yield 65%. White solid. ^{1}H NMR: (CDCl$_3$, 300 MHz): δ 7.38 (d, J = 7.95 Hz, 4H); 7.18 (d, J = 7.86 Hz, 4H); 6.95 (dd, J = 12.0, 2.65 Hz, 2H); 6.66 (dd, J = 12.0, 2.91, 2H); 2.39 (s, 6H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 137.36, 134.72, 132.26, 129.38, 128.51, 126.25, 21.26. MS 234 (82); 219 (100); 204 (49); 115 (24); 105 (47); 77 (21).
12. *General procedure for all cross-coupling reactions*: A two-necked 50-mL flask under a nitrogen atmosphere was charged with potassium 4-methyl styryltrifluoroborate (0.5 mmol, 0.112 g), potassium 4-bromo styryltrifluoroborate (0.5 mmol; 14.4 mg), Pd(OAc)$_2$ (15 mol %, 16.50 mg), Ag$_2$O (3 equiv, 34.76 mg), and DMSO (3 mL). The reaction mixture was heated at 70 °C for 7 h, and the reaction was followed by TLC. After completion, the reaction mixture was allowed to reach rt and then NH$_4$Cl (30 mL) was added, and the organic phase was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, dried (MgSO$_4$), and the solvent was removed under vacuum to provide a viscous yellow oil. The oil was purified by column chromatography using a mixture of hexane/ethyl acetate (96:4) as the eluent to afford the solid products (see Table 3, entry 4: 38%—MS = 206 (100), 191 (40), 128 (36), 91 (71), 77 (17); 32%—MS = 284 (56), 205 (100), 190 (25), 128 (27), 101 (37), 89 (33); 30%—MS = 204 (100), 101 (27), 89 (17), 76 (14).