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A New Synthesis of Butadienyl- and Styrylboronic Esters: Highly Reactive Intermediates for Suzuki Cross-Coupling

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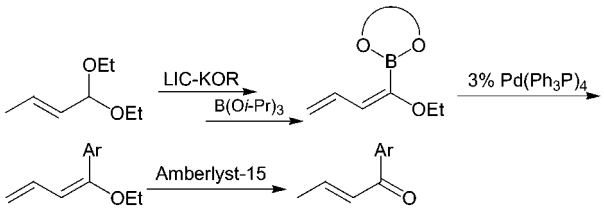
ABSTRACT



Alkoxy-functionalized butadienyl- and styrylboronic esters have been synthesized starting from α,β-unsaturated acetals. These derivatives readily cross-couple with aryl substrates, and the obtained products can be transformed under mild conditions into aromatic ketones, achieving the same result as an acylation reaction.

The Pd(0)-catalyzed cross-coupling reaction has become one of the most popular methods of accessing biaryls, and in particular the Suzuki−Miyaura reaction, using arylboronic acid, has emerged as one of the most widely used.[1] As compared with the Stille cross-coupling,[2] the Suzuki process possesses the advantage that byproducts are nontoxic and are easily separated from the target product.[3] Catalyst systems that allow coupling with aryl chlorides have been developed, greatly expanding the scope of the reaction.[4] Traditionally, arylboronic acids have been prepared by reaction of an aryllithium derivative, obtained by metal−halogen or metal−hydrogen exchange, with trialkylborates.[5] Moreover, it has been recently reported that the in situ trapping with triisopropylborate of lithium intermediates is an excellent reagent system for the synthesis of substituted arylboronic esters, which were isolated as 2,2-dimethylpropan-1,3-diol (neopentyl glycol) adducts.[6] Although the Suzuki cross-coupling is commonly used to prepare biaryls, reactions of vinyl halides or triflates with arylboronic acids, to generate styrene derivatives, are an important and interesting broadening of the method. Much attention has been also focused on the use of 1-alkenylboronic acids or their esters, because of the variety 1-alkenylboron derivatives that are readily available by stereodefined hydroboration reaction of alkynes.[7] In particular, 1,3-dienylboronates have been prepared by a three-step sequence starting from the hydroboration of enynes with

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(1) For reviews, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263−303. Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.

(2) Stille, J. K.; Milstein, D. *J. Am. Chem. Soc.* **1978**, *100*, 3636−3638. For reviews, see: Stille, J. K. *Angew. Chem., Int. Ed Engl.* **1986**, *25*, 508−524. Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73−78. Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

(3) Boyer, J. *Toxicology* **1989**, *55*, 253−298.

(4) Littke, F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387−3388. Wolfe, J. P.; Buchwald, L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2414. Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R., Jr. *Org. Lett.* **2001**, *3*, 1555−1557.

(5) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763−3768. Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 49−64.

(6) Kristensen, J.; Lysén, M.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435−1437.

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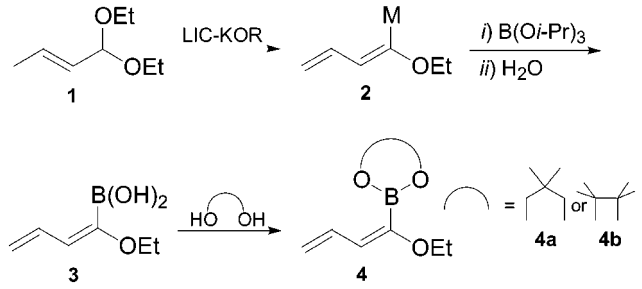
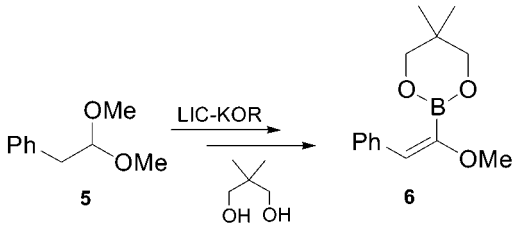
Scheme 1



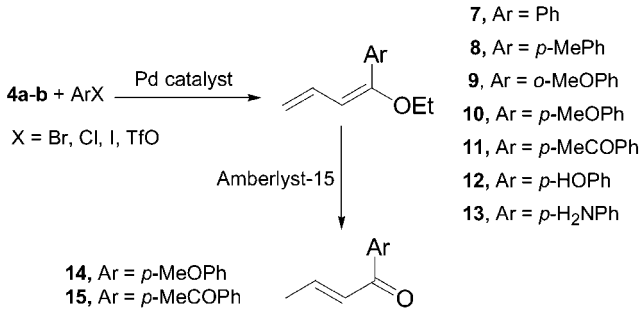
various hydroborating agents.[8] Moreover, as stated by Molander and Ito,[9] much of the recent development of the Suzuki coupling reaction has focused on metal catalysts rather than on expanding the range of organoboron coupling partners, which should be an equally important endeavor.

The synthesis of polyenic structures has been of great interest to organic chemistry owing not only to their presence in natural products[10] but also to their importance as useful chemicals in the perfume industry and other fields.[11] Our interest in the synthesis of stereodefined substituted dienes required the development of diverse organometallic reagents and protocols for the preparation of key building blocks.[12] In the course of these studies we have set up a new synthesis of alkoxy-functionalized butadienyl- and styrylboronic esters,[13] and resorting to the particular reactivity of these derivatives, we have successfully carried out their cross-coupling with various aryl halides and triflates under very mild experimental conditions (Schemes 1 and 2). Furthermore, the method we have set up allows us to achieve coupling products suitably functionalized to undergo additional synthetic modifications; namely, the sequence "cross-coupling and hydrolysis" corresponds to a two-step carbonylative coupling (Schemes 3 and 4).[14]

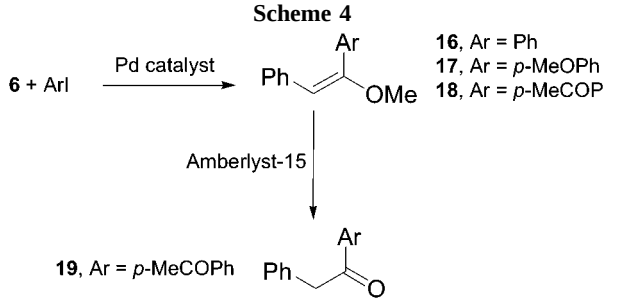
Scheme 2



Scheme 3



Scheme 4



Treatment of crotonaldehyde diethyl acetal (**1**) at −95 °C with Schlosser's LIC−KOR base (LIC, butyllithium; KOR, potassium *tert*-butoxide)[15] readily gives α-metalated 1-ethoxybuta-1,3-diene (**2**). Subsequent reaction with triisopropylborate leads to immediate disappearance of the deep red color due to metalated diene. Aqueous workup of the reaction mixture affords intermediate **3**, which owing to its instability was trapped with 2,2-dimethylpropane-1,3-diol or 2,3-dimethylbutane-2,3-diol, giving the corresponding boronic ester **4a** or **4b**, respectively (Scheme 1).

Resorting to an analogous synthetic design styrylboronic ester **6** has been prepared starting from phenyl acetaldehyde dimethyl acetal **5** (Scheme 2).

As outlined in Table 1, the cross-coupling reaction of butadienyl and styrylboronic esters proceeds with satisfactory

(7) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975. Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370−437. Lane, C. F. *Tetrahedron* **1976**, *32*, 981−990. Colberg, J. C.; Rane, A.; Soderquist, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 6065−6071.

(8) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R. W.; Denne, I. *Tetrahedron Lett.* **1987**, *28*, 4169−4172. Renard, P.-Y.; Lallemand, J.-Y. *Tetrahedron*: *Asymmetry* **1996**, *9*, 2523−2424. Six, Y.; Lallemand, J.-Y. *Tetrahedron Lett.* **1999**, *40*, 1295−1296 and references therein.

(9) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393−396.

(10) Baker, R.; Bradshaw J. W. S. In *Aliphatic and Related Natural Product Chemistry*; Gunstone, F. D., Ed.; Specialist Periodical Report, Royal Society of Chemistry: London, 1983; Vol. 3. Nicolau, K. C.; Ramphal, J. Y.; Petasis, N. A.; Serhan, C. N. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1100−1116. Launay, V.; Beaudet, I.; Quintard, J.-P. *Bull. Soc. Chim. Fr.* **1997**, *134*, 937−946. Dominguez, B.; Iglesia, B.; de Lera, A. R. *J. Org. Chem.* **1998**, *63*, 4135−4139. Lipshutz, B. H.; Ullman, B.; Lindsley, C.; Pecchi, S.; Buzard, D. J.; Dickson, D. *J. Org. Chem.* **1998**, *63*, 6092−6093.

(11) Goldbach, M.; Jäkel, E.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1987**, 1434−1435.

(12) Venturello, P. *J. Chem. Soc., Chem. Commun.* **1992**, 1032−1033. Balma Tivola, P.; Deagostino, A.; Prandi, C.; Venturello, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 437−441 and references therein.

(13) Owing to the different mechanism, boronic esters have been obtained with the double bond configuration opposite to that from the hydroboration reaction of alkynes.

(14) Wakita, Y.; Yasunaga, T.; Akita, M.; Kojima, M. *J. Organomet. Chem.* **1986**, *301*, C17−C20. Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 7661−7664.

(15) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9−16. Schlosser, M. *Mod. Synth. Methods* **1992**, *6*, 227−271. Mordini, A. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI Press Inc.: Greenwich, CT, 1992; Vol. 1, pp 1−45. Schlosser, M.; Faigl, F.; Franzini, L.; Geneste, H.; Katsoulos, G.; Zhong, G. *Pure Appl. Chem.* **1994**, *66*, 1439−1446. Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, 1115−1126.

Table 1. Cross-Coupling Reaction of Butadienyl (**4a** and **4b**) and Styrylboronic (**6**) Esters with Various Aryl Halides and Triflates[a]

entry	substrate	boronic ester	product	reaction conditions[b] (°C)	yield (%)[c]
1	PhI	**4a**	**7**	A (25)	82
2	PhI	**4b**	**7**	A (25)	71
3	PhI	**6**	**16**	A (25)	88
4	*o*-MeOPhI	**4a**	**9**	A (25)	75
5	*p*-MeOPhI	**4a**	**10**	A (25)	70
6	*p*-MeOPhI	**4b**	**10**	A (25)	89
7	*p*-MeOPhI	**6**	**17**	A (25)	92
8	*p*-MeCOPhI	**4a**	**11**	A (25)	90
9	*p*-MeCOPhI	**4a**	**11**	B (25)	78
10	*p*-MeCOPhI	**4b**	**11**	A (25)	83
11	*p*-MeCOPhI	**6**	**18**	A (25)	85
12	*p*-MeCOPhI	**6**	**18**	B (25)	65
13	*p*-HOPhI	**4a**	**12**	A (25)	75
14	*p*-H_2NPhI	**4a**	**13**	A (25)	90
15	PhBr	**4a**	**7**	A (25)	30
16	PhBr	**4a**	**7**	A (60)	83
17	*p*-MeOPhCl	**4a**	**10**	B (25)	10
18	*p*-MeOPhCl	**4a**	**10**	C (60)	20
19	*p*-MeCOPhCl	**4a**	**11**	C (25)	45
20	*p*-MePhOTf	**4a**	**8**	A (25)	85

[a] The spectral data for all new compounds are consistent the structures proposed. [b] A = $[(C_6H_5)_3P]_4Pd$, aqueous (2 M) K_2CO_3, toluene; B = $[(C_6H_5CH{=}CH)_2CO]_3Pd_2$, (*o*-$CH_3C_6H_4)_3P$, KF, THF; C = $[(C_6H_5CH{=}CH)_2CO]_3Pd_2$, (*o*-$CH_3C_6H_4)_3P$, aqueous (2 M) K_2CO_3, THF. [c] Isolated and purified products.

yields in most cases, regardless of the electronic character of the aryl iodides (compare, for instance, entries 1, 4, and 8 or 3, 7, and 11).

Although we have not attempted to improve the yields by modifying the reaction conditions (i.e., catalyst and/or phosphine) and have worked in the presence of triarylphosphines,[16] cross-coupling products have been obtained even with electron−neutral aryl bromide (entries 15 and 16), in moderate yield with electron-poor aryl chlorides (entry 19), and in very low yields with electron-rich aryl chlorides (entries 17 and 18).

We have successively carried out the hydrolysis of the cross-coupling derivatives **10**, **11**, and **18** and prepared the corresponding carbonyl derivatives **14**, **15**, and **19** with excellent yields, under very mild conditions (Schemes 3 and 4 and Table 2), achieving the very same result as an acylation of activated and deactivated aromatic substrates.[17]

(16) G. C. Fu and A. F. Littke have proved that triarylphosphines result in ineffective ligands in Suzuki cross-coupling of aryl chlorides (see ref 4).

(17) **Typical Procedure.** To a cooled solution (−95 °C) of *t*-BuOK (1.4 g, 12.5 mmol) in anhydrous THF (10 mL) were consecutively added acetal **1** (0.72 g, 5.0 mmol) and BuLi (7.8 mL, 12.5 mmol) dropwise under stirring. After 2 h the purple-red solution was treated with triisopropylborate (10.0 mmol, 2.4 mL). The solution was allowed to warm to 25 °C and then quenched with saturated aqueous NH_4Cl (10 mL). The organic phase was diluted with Et_2O and then washed with brine. After anhydrification (Na_2SO_4) and evaporation of the solvent, the crude product was diluted with toluene (30 mL) and treated with 2,2-dimethyl-1,3-propandiol (5 mmol, 0.52 g). The mixture was stirred at 25 °C overnight under an inert atmosphere. The organic phase was diluted with diethyl ether and washed with water. Drying (Na_2SO_4) and removal of the solvent gave 0.98 g (93%) of analytically pure (*E*)-2-[(1-ethoxy)buta-1,3-dienyl]-5,5-dimethyl-[1,3,2]-dioxaborinane (**4a**) as a pale yellow oil: ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.94 (s, 6 H), 1.28 (t, J = 6.5 Hz, 3 H), 3.67 (s, 4 H), 3.72 (q, J = 6.5 Hz, 2 H), 4.86 (dd, J = 10.0, 1.0, 1 H), 5.03 (dd, J = 16.0, 1.0, 1 H), 5.97 (d, J = 10.0 Hz, 1 H), 7.04 (dt, J = 16.0, 10.0 Hz, 1 H); ^{13}C NMR (100.4 MHz; $CDCl_3$) δ 15.28, 21.86, 31.66, 62.50, 72.27, 113.92, 116.76, 118.22, 134.06; MS (EI, 70 eV) *m*/*z* (%) 210 (30), 181 (48), 113 (19), 95 (28), 69 (100). Under an inert atmosphere the boronic ester **4a** (0.5 mmol, 0.10 g) was dissolved in toluene (5 mL), and then aqueous 2 M K_2CO_3 (0.5 mL), *p*-$MeOC_6H_4I$ (0.6 mmol, 0.14 g), EtOH (0.5 mL), and $Pd[(C_6H_5)_3P]_4$ (3%, 17 mg) were added. The reaction mixture was stirred at 25 °C to completeness (TLC or GC control). Addition of saturated aqueous NH_4Cl (5 mL) followed by extraction with Et_2O, drying (Na_2SO_4), and evaporation under vacuum provided crude 1-(1-ethoxybuta-1,3-dienyl)-4-methoxybenzene (**10**), which was purified by column chromatography (petroleum ether/Et_2O 8:2) (70 mg, 70%): ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.28 (t, J = 6.5 Hz, 3 H),), 3.82 (s, 3 H), 3.92 (q, J = 6.5 Hz, 2 H), 4.79 (dd, J = 10.0, 1.0 Hz, 1 H), 5.09 (dd, J = 16.0, 1.0 Hz, 1 H), 5.56 (d, J = 10.0 Hz, 1 H), 6.45 (dt, J = 16.0, 10.0 Hz, 1 H), 6.69 (d, J = 7 Hz, 2H), 7.38 (d, J = 7 Hz, 2 H); ^{13}C NMR (100.4 MHz; $CDCl_3$) δ 14.80, 55.37, 63.49, 102.84, 111.77, 113.45, 116.42, 130.48, 134.17, 138.25, 157.83, 159.82; MS (EI, 70 eV) *m*/*z* (%) 204 (52), 173 (31), 159 (99), 135 (84), 115 (65). Amberlyst 15 (4.6 mequiv/g, 37 mg) was suspended in CH_3Cl (10 mL), and the substrate **10** (5.0 mmol, 010 g) was added with stirring at 25 °C. After 30 min the resin was filtered off, and the reaction mixture was treated with K_2CO_3, filtered, and concentrated under vacuum to give crude 1-(4-methoxyphenyl)-but-2-en-1-one (**14**), which was purified by column chromatography (petroleum ether/Et_2O 8:2) (0.08 g, 90%):^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (dd, J = 6.5, 1.5 Hz, 3 H), 3.90 (s, 3 H), 6.80 (dq, J = 15, 1.5 Hz, 1 H), 6.89 (d, J = 7.2 Hz, 2 H), 6.94 (dq, J = 15, 6.5, 1 H), 7.94 (d, J = 7.2 Hz, 2 H); ^{13}C NMR (100.4 MHz; $CDCl_3$) δ 18.4, 55.53, 113.79, 127.19, 129.10, 130.87, 144.03, 163.33, 189.07; MS (EI, 70 eV) *m*/*z* (%) 176 (M^+, 42), 135 (100), 77 (31), 69 (14), 63 (15), 41 (19).

Table 2. Hydrolysis of Functionalized Cross-Coupling Derivatives[a]

entry	cross-coupling product	ketone	yield (%)[b]
1	**10**	**14**	90
2	**11**	**15**	87
3	**18**	**19**	95

[a] The spectral data for all new compounds are consistent the structures proposed. [b] Isolated and purified products.

In summary, we have developed a new method for the synthesis of organoborates that cross-couple effectively with a broad spectrum of aryl substrates. This method should be useful in synthetic organic chemistry because of the accessibility of starting material. Additionally, we have reported that butadienyl- and styrylboronic esters can be coupled under mild conditions. Moreover, the present method thus provides a new and effective approach to functionalized aromatic ketones.

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