

Zr-Mediated hydroboration: stereoselective synthesis of vinyl boronic esters

Yanong D. Wang,^{a,*} Gregory Kimball,^b Amar S. Prashad^a and Yan Wang^a

^aChemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, USA

^bDepartment of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, USA

Received 8 September 2005; accepted 11 October 2005

Abstract—An improved process for the preparation of (*E*)-vinylboronic esters via a Zr-mediated hydroboration of alkynes, especially oxygen-containing alkynes, is described.

© 2005 Published by Elsevier Ltd.

The formation of new asymmetric carbon–carbon bonds can be accomplished readily using a wide range of palladium-catalyzed cross coupling reactions^{1–3} that have also been utilized extensively in the construction of biologically active molecules.⁴ One of these processes involves the cross coupling reaction of an organometallic derivative with an alkyl or aryl halide, with organoborane derivatives being especially useful.^{5,6} As one type of frequently used synthetic building block, vinylboronic esters can be prepared by several methods,^{7–10} particularly by hydroboration of alkynes using catecholborane,^{11,12} which often requires harsh reaction conditions. In 1992, Knochel and co-workers¹³ reported the preparation of pinacolborane. It was also shown that pinacolborane is an efficient hydroboration reagent, which offers advantages of mild reaction conditions, high functional group tolerance, and excellent stability over catecholborane.

The transition metal complex catalyzed hydroboration of alkynes has been investigated considerably, including development of new methodologies and mechanistic studies.^{14–18} Pereira and Srebnik reported¹⁵ that the Schwartz reagent (Cp₂ZrHCl) catalyzes hydroboration of alkynes with pinacolborane at room temperature. In the process high selectivity of syn addition and regioselectivity were observed. However, the hydroboration of some less reactive alkynes can be sluggish, and the stereoselectivity toward *E*-vinylboronic esters is unsatisfactory, especially for oxygen-containing alkynes.

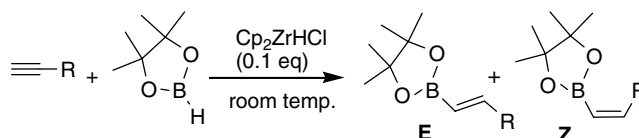
We present here a modified protocol of Zr-mediated hydroboration, which offers (*E*)-vinylboronic esters in high yield as well as excellent stereoselectivity and regioselectivity.

In general, hydroboration of hydrocarbon alkynes all proceeded smoothly at ambient temperature, in the absence of solvent (Table 1). Formation of the (*Z*)-isomer was observed for alkynes substituted by less bulky groups in negligible quantities.

Hydroboration of oxygen-containing alkynes (Table 2) was rather sluggish compared to the hydrocarbon alkynes. The *E/Z* ratio of the hydroboration products dramatically decreased, especially for the alkynes with longer linkers between the alkyne and oxygen atom.

Zr-Mediated hydroboration of alkynes is believed to operate by a pathway involving alkyne insertion, σ -bond

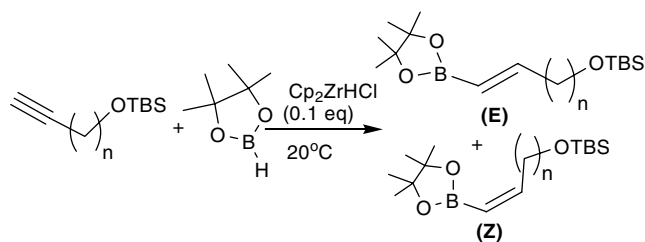
Table 1.



R	Yield (%)	<i>E</i>	<i>Z</i>
<i>n</i> -Butyl	90	97	3
Cyclohexyl	86	98	2
Phenyl	96	98	2
<i>tert</i> -Butyl	58	100	0

* Corresponding author. Tel.: +1 845 602 5253; fax: +1 845 602 5561; e-mail: wangd@wyeth.com

Table 2.



<i>n</i>	Yield (%)	<i>E</i>	<i>Z</i>
1	79	95	5
2	62	90	10
3	63	79	21
4	66	62	38
9	37	54	46

metathesis, and vinyl–hydride exchange, similar to the mechanism of lanthanide-catalyzed hydroboration of alkenes,^{17,18} as shown in Figure 1.

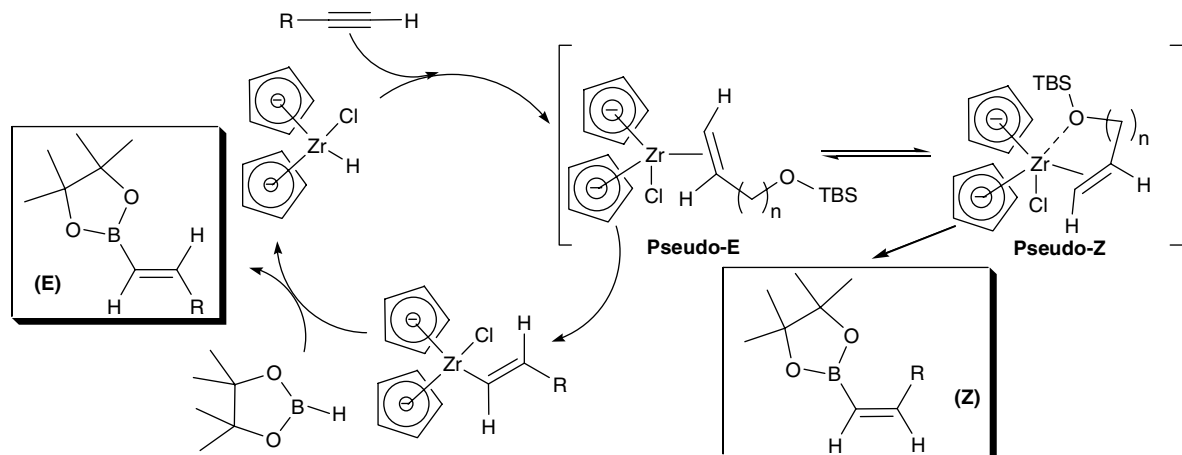
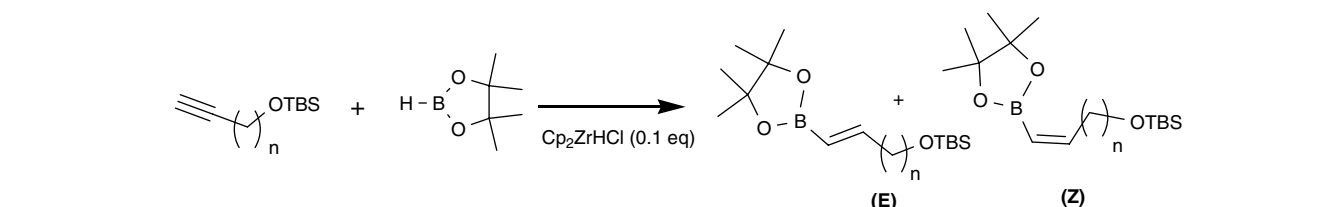


Figure 1.

Table 3.



<i>n</i>	Additive	Reaction time (h)	Reaction temperature	Yield (%)	<i>E</i>	<i>Z</i>
4	None	20	rt	66	62	38
2	None	20	rt	62	90	10
4	1.0 equiv BF ₃ –Et ₂ O	20	rt	<5	74	26
4	1.0 equiv Et ₃ N	20	rt	19	82	18
4	0.1 equiv pyridine	20	rt	45	54	46
4	0.1 equiv DMAP	20	rt	10	79	21
4	0.1 equiv Et ₃ N	20	rt	41	93	7
4	None	16	60 °C	94	96	4
2	None	16	60 °C	93	95	5
4	0.1 equiv Et ₃ N	16	60 °C	94	98	2
2	0.1 equiv Et ₃ N	16	60 °C	96	98	2

It is speculated that the intramolecular interaction between the 16-electron bis(cyclopentadienyl)-zirconium center and oxygen favors the formation of a pseudo-(*Z*) intermediate, which in turn leads to the formation of (*Z*)-vinylboronic esters, as shown in Figure 1. The longer the linker between the alkyne and oxygen atom is, the more likely the formation of the pseudo-(*Z*) intermediate.

This prompted us to investigate practical modifications to disrupt this hypothesized intramolecular O–Zr interaction in order to improve the stereoselectivity and yield toward (*E*)-vinylboronic esters. Therefore, a Lewis acid and base, targeting either the oxygen or zirconium site, respectively, were examined. While a Lewis acid (BF₃–Et₂O) had limited impact on the outcome of hydroboration, the base Et₃N improved the stereoselectivity considerably (Table 3). A catalytic amount of Et₃N appeared to work better than a stoichiometric amount on both yield and stereoselectivity (Et₃N > DMAP > pyridine), though it gave a lower yield of vinylboronic

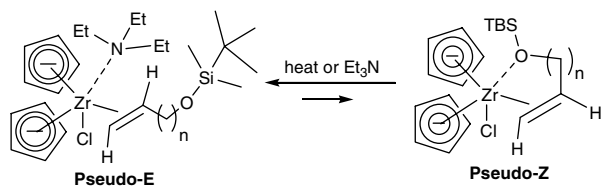


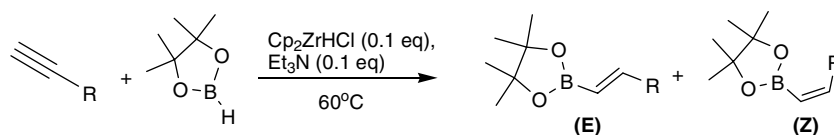
Figure 2.

ester than hydroboration without amine. We then looked at the possibility of a thermal intervention of the intramolecular Zr–O interaction. We found that hydroboration at an elevated temperature indeed afforded (*E*)-vinylboronic esters with better stereoselectivity and yield than reaction at ambient temperature. Furthermore, hydroboration at an elevated temperature in the presence of a catalytic amount of Et₃N resulted in an optimal outcome in both stereoselectivity and yield (Fig. 2).

We carried out the hydroborations of alkynes substituted by various functional groups using this protocol (Table 4).¹⁹ They all proceeded smoothly to afford the corresponding (*E*)-vinylboronic esters in both good yield and stereoselectivity.

In summary, a robust and mild reaction protocol was developed for the hydroboration of alkynes to give *E*-vinylboronic esters in good to excellent yield (59–99%). High stereoselectivity (*E/Z* > 95:5) and regioselectivity were achieved. This new protocol showed high tolerance for various functional groups on the alkynes. An intramolecular interaction between the 16-electron zirconium center and oxygen atom was proposed based on the experimental results observed in the Zr-mediated hydroboration reaction of oxygen-containing alkynes.

Table 4.



Entry	R	Yield (%)	<i>E</i>	<i>Z</i>
1		90	98	2
2		96	98	2
3		92	96	4
4		94	98	2
5		93	99	1
6		99	100	0
7		76	96	4
8		59	97	3
9		95	100	0
10		90	100	0
11		99	98	2

Acknowledgments

We thank the Chemical Technologies group at Wyeth Research, Pearl River, NY for spectral and combustion analyses. We also thank Drs. Diane H. Boschelli, Dennis Powell and Tarek Mansour for their support of this work.

References and notes

1. Tsuji, T. *Palladium Reagents and Catalysts: Innovation in Organic Chemistry*; John Wiley & Sons: Chichester, 1995.
2. Malleron, J. L.; Fiaud, J. C.; Legros, J. Y. *Handbook of Palladium Catalyzed Organic Reactions: Synthetic Aspects and Catalytic Cycles*; Academic Press, 1997; p 1.
3. Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; p 49.
4. Larsen, R. D. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 651.
5. Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419.
6. Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, *8*, 1405.
7. Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535.
8. Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
9. Hoffmann, R. W.; Dresely, S. *Synthesis* **1988**, *2*, 103.
10. Brown, H. C.; Rucherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868.
11. Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1971**, *93*, 1816.
12. Lane, C. F.; Kabalka, G. W. *Tetrahedron* **1976**, *32*, 981.
13. Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.
14. He, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 1696.
15. Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127.

16. Hartwig, J. F.; Muhoro, C. N.; He, X.; Eisenstein, O.; Booque, R.; Maseras, F. *J. Am. Chem. Soc.* **1996**, *118*, 10936.
17. Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283.
18. Harrison, K. N.; Marks, T. J. *J. Org. Chem.* **1992**, *114*, 9220.
19. General procedure: To a mixture of *tert*-butyl-but-3-ynyloxy-dimethylsilane (1.0 g, 7.14 mmol)²⁰ and 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (958 mg, 7.49 mmol) was added bis(cyclopentadienyl)zirconium chloride hydride (183 mg, 0.714 mmol) and triethylamine (72 mg, 0.714 mmol). The resulting mixture was heated at 60 °C for 16 h and diluted with hexanes. The precipitate was removed by filtering over a short pad of silica gel and washed with hexanes. The filtrate was concentrated and dried in vacuum to give 1.76 g (93% yield) of *tert*-butyl(dimethyl){[(*5E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl]oxy}silane as a colorless liquid.
20. Pereira, R.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **2001**, *57*, 7871.