Tetrahedron Letters, Vol.31, No.45, pp 6509-6512, 1990
Printed in Great Britain

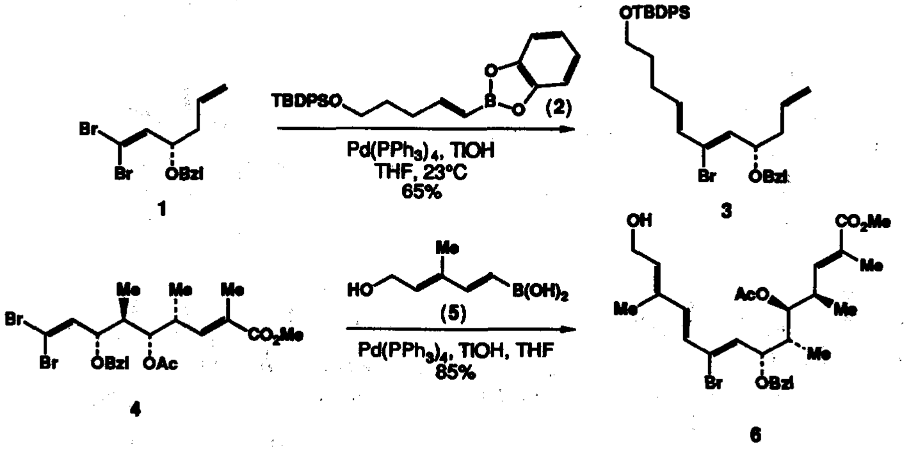
0040-4039/90 $3.00 + .00
Pergamon Press plc

STEREOSELECTIVE SYNTHESIS OF (Z,E)-2-BROMO-1,3-DIENES VIA THE PALLADIUM (O) CATALYZED CROSS COUPLING REACTIONS OF 1,1-DIBROMOOLEFINS AND VINYLBORONIC ACIDS

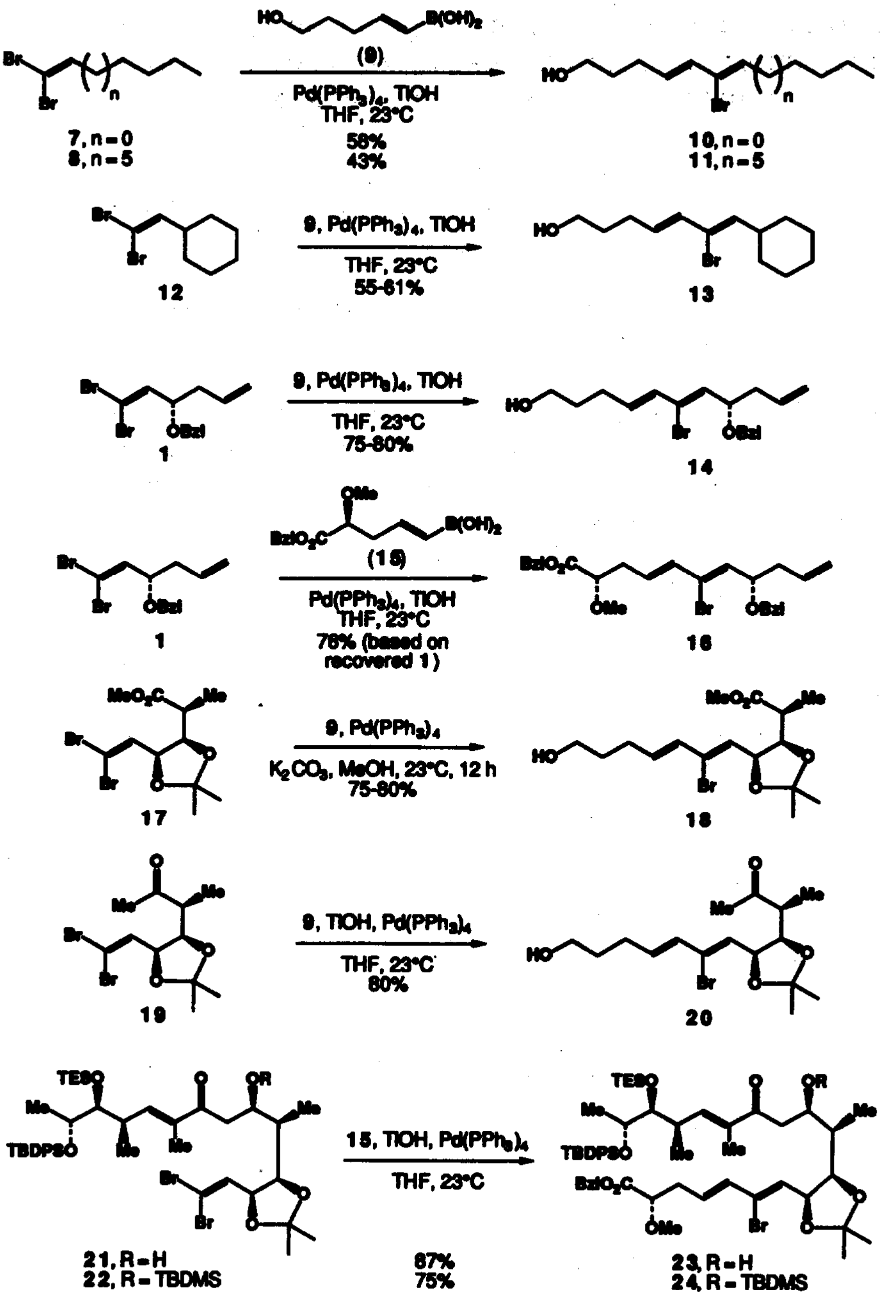
William R. Roush,* Kevin J. Moriarty and Bradley B. Brown
Department of Chemistry, Indiana University, Bloomington, IN 47405

Abstract. (Z,E)-2-Bromo-1,3-dienes are synthesized via stereoselective Pd° catalyzed cross coupling reactions of 1,1-dibromoolefins and vinylboronic acids.

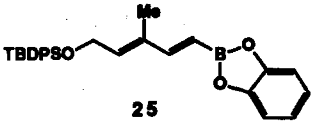
We have recently found it advantageous to utilize (Z,E)-2-bromo-1,3-dienes as the diene components in several intramolecular Diels-Alder reactions.[1] Because 2-bromo-1,3-dienes are not conveniently prepared by using conventional Wittig methodology,[1a] we have explored a direct and potentially more efficient approach based on the Pd° catalyzed cross coupling reactions of 1,1-dibromoolefins and vinylboronic acid derivatives (i.e., modified Suzuki cross coupling reactions).[2] We reasoned that selective cross-couplings should be possible since it was already known that the rates of palladium catalyzed cross-coupling reactions of (E)- and (Z)-1-bromoalkenes are substantially different.[3] Subsequent to the initiation of our work several other classes of selective palladium catalyzed mono cross coupling reactions of 1,1-dihaloolefins have been described.[4] We have demonstrated the applicability of the modified Suzuki cross coupling technology in syntheses of 3 and 6,[1b,c] and report herein additional examples and comment on the scope of this methodology for the stereoselective synthesis of (Z,E)-2-bromo-1,3-dienes.



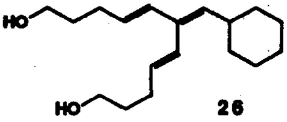
In our initial report on the synthesis of 3 we noted that the yield was only 36% using standard Suzuki cross coupling conditions (aqueous NaOH, C_6H_6, reflux), and that considerable improvements were achieved by using the TlOH modification introduced by Kishi and coworkers.[1b,2b] We have subsequently found that the reactions are further improved when vinylboronic acids are employed rather than the catechol borane derivatives. Thus, for example, the cross coupling of 1 and vinylboronic acid 9 proceeds in 75-80% yield


7, n = 0
8, n = 5
(9)
Pd(PPh$_3$)$_4$, TlOH
THF, 23°C
58%
43%
10, n = 0
11, n = 5
12
9, Pd(PPh$_3$)$_4$, TlOH
THF, 23°C
55-61%
13
1
9, Pd(PPh$_3$)$_4$, TlOH
THF, 23°C
75-80%
14
1
(15)
Pd(PPh$_3$)$_4$, TlOH
THF, 23°C
76% (based on recovered 1)
16
17
9, Pd(PPh$_3$)$_4$
K$_2$CO$_3$, MeOH, 23°C, 12 h
75-80%
18
19
9, TlOH, Pd(PPh$_3$)$_4$
THF, 23°C
80%
20
21, R = H
22, R = TBDMS
15, TlOH, Pd(PPh$_3$)$_4$
THF, 23°C
87%
75%
23, R = H
24, R = TBDMS

(92% when corrected for recovered 1) compared to a maximum of 65% using the catechol vinylboronate 2, while the cross coupling of 4 and the fully protected catechol boronate derivative 25 proceeds in highly variable and nonreproducible yields (10-65%), compared to 85% obtained when the unprotected dienylboronic acid 5 is used. We suspect that the reactions involving the vinylboronic acids are more efficient since they are easier to purify than the catechol ester derivatives and the quality of the reagents utilized is more consistent.



25



26

The following procedure is representative. A mixture of 384 mg (0.45 mmol) of dibromide 21[5] and 192 mg (0.56 mmol, 1.25 equiv.) of vinylboronic acid 15[6] in 4 mL of dry THF under N_2 was treated with 52 mg (0.045 mmol, 0.10 equiv.) of $(Ph_3P)_4Pd$ for 10 min at 23°C, and then 1.13 mL of a 0.4 M solution of TlOH in H_2O (0.45 mmol, 1.0 equiv.) was added via syringe. The solution was stirred at 23°C for 5 min, then it was diluted with hexane and dried over $MgSO_4$. The mixture was filtered and the crude product was purified by flash chromatography (1 : 1 hexane-Et_2O) giving 421 mg (87%) of bromo triene 23. The majority of the cross coupling experiments summarized in the Table were preformed by using this procedure. Very good results also were obtained in one experiment using K_2CO_3 in MeOH (the coupling of 17 and 9 that provided 18 in 75-80% yield), indicating that use of TlOH may not be obligatory in all cases. The reactions performed with TlOH are extremely rapid, however, and this certainly may be advantageous in many cases.[2b]

It is noteworthy that single products are observed in each of the cross coupling experiments involving dibromoolefins 1, 4, 17, 19, 21 and 22. The (Z,E)-diene stereochemistry was assigned in the cases of 3, 6, and 18 on the basis of their ready participation in subsequent intramolecular Diels-Alder reactions.[1] It is also of interest that this cross coupling reaction is compatible with a high degree of functionality in both the dibromoolefin as well as the vinylboronic acid units. For example, potentially base sensitive (i.e., epimerizable) stereocenters α to methyl ketones or carboalkoxyl groups, as in 15, 17, 19 and the derived coupling products, survive the cross coupling reaction without complication, and even unprotected aldols (e.g., 21, 23) are acceptable structural units. The TlOH promoted cross couplings are also sufficiently rapid, and therefore mild, that competitive hydrolysis of base labile protecting groups such as acetates (c.f., 6) and carboxylic esters (c.f., benzyl esters in 16 and 23-24) is not a significant complication.

A structural feature common to the dibromoolefins 1, 4, 17, 19, 21 and 22 that undergo the most efficient and highly stereoselective cross couplings is an allylic alkoxy group. We suspected initially that the excellent stereoselectivity in these reactions was due to the differential steric environments of the (Z)- vs. (E)-bromo groups of the dibromoolefin substrates. Analogous cross coupling reactions of dibromoolefins 7, 8, and 12 were thus examined to probe this hypothesis. While these substrates readily react with vinylboronic acid 9 under standard conditions (1.5 equiv. of 9, 0.1 equiv. of $Pd(PPh_3)_4$, 1.0 eq. TlOH, THF, 23°C), the yields of bromo dienes 10, 11, and 13 are only moderate (43-61%) and several additional products are also produced. Among these are the dicoupled trienes (26 in the case of 12) that have been isolated in 5-10% yield from several different experiments. These products do not appear to arise via secondary cross couplings of the

(Z)-2-bromo-1,3-diene products, since subjection of **11** and **13** to the original reaction conditions gave at most only traces of the dicoupled materials (TLC analysis); ca. 80% of **11** and **13** was recovered from these experiments. It may well be then that secondary products such as **26** derive from an initial cross coupling at the (Z)-bromo unit of **7**, **8**, or **12**, with the resulting (E)-2-bromo-1,3-diene (that is presumably more reactive than the (Z)-diene isomer for steric reasons) then undergoing a second cross coupling to give the observed 2 : 1 adducts. In retrospect, it appears that the allylic alkoxy substituents of the most efficient dibromoolefin substrates contribute both a steric as well as an electronic component that have a beneficial influence on the outcome of these modified Suzuki cross coupling reactions.

In summary, the modified Suzuki cross coupling of 1,1-dibromoolefins and vinylboronic acids constitutes a convenient means of synthesizing (Z,E)-2-bromo-1,3-dienes. The stereoselectivity is excellent in all cases examined, and the reactions are most efficient when 1,1-dibromoolefins possessing allylic alkoxy substituents are employed. The reactions are also compatible with a wide range of potentially base sensitive functionality. Several of the (Z,E)-2-bromo-1,3-dienes described in this Letter are intermediates in ongoing synthetic studies, and future reports will describe our progress along those lines.

Acknowledgement: This research was supported by a grant from the National Institute of General Medical Sciences (GM 26782).

References

1. (a) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, 26, 4327. (b) Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, 53, 710. (c) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, 29, 3541.
2. For leading references, see: (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, 107, 972. (b) Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *Ibid.* **1987**, 109, 4756. (c) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *Ibid.* **1989**, 111, 314.
3. Carpita, A.; Rossi, R. *Tetrahedron Lett.* **1986**, 27, 2529.
4. (a) Ratovelomanana, V.; Hammoud, A.; Linstrumelle, G. *Tetrahedron Lett.* **1987**, 28, 1649. (b) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, 109, 1257. (c) Trost, B. M.; Walchli, R. *Ibid.* **1987**, 109, 3487 (an intramolecular cross coupling of a 1,1-dibromoolefin).
5. Dibromoolefins **1**, **4**, **7**, **8**, **12**, and **17** were synthesized from the corresponding aldehydes by use of the Corey-Fuchs dibromoolefination procedure: Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. The syntheses of **19** and especially **21** and **22** involve several operations after introduction of the dibromoolefin units, and will be described in detail elsewhere.
6. Vinylboronic acids **9** and **15** were prepared in 65-70% yields by hydroboration of the corresponding acetylenes with catecholborane (neat, 100°C) and were purified by silica gel chromatography.

(Received in USA 7 August 1990)