Pergamon

Tetrahedron Letters 40 (1999) 4589–4592

TETRAHEDRON
LETTERS

The C-2 Selective Azide Opening Reaction of *trans*-2,3-Epoxy Alcohols by NaN_3 and $PhB(OH)_2$

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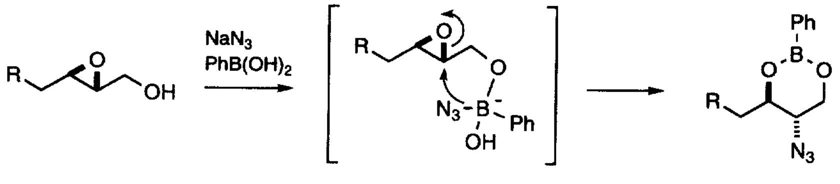
Received 18 March 1999; revised 12 April 1999; accepted 16 April 1999

Abstract: The azide opening reaction of *trans*-2,3-epoxy alcohols with NaN_3 and $PhB(OH)_2$ in DMF occurred regio- and stereoselectively at the C-2 position giving rise to phenylboronates of *trans*-2-azido-1,3-diols in high yields.

Stereoselective epoxide-opening reactions have been recognized as one of the most important transformations in organic synthesis.[1] Among them, the azide opening reaction of 2,3-epoxy alcohols has gained importance in context with the synthesis of biologically active molecules.[2] Although various methods / reagents such as Me_3SiN_3-Et_2AlF,[3] NaN_3-NH_4Cl,[4] NaN_3 supported on calcium zeolite,[5] [Ti(O-*i*-Pr)$_2$(N_3)$_2$],[6] Bu_3SnN_3,[7] Ti(O-*i*-Pr)$_4$-Me_3SiN_3,[8] Et_2AlN_3,[9] etc. have been developed for the purpose, the regioselectivity in these azide opening reactions is restricted only at the C-3 position. On the other hand, examples pertaining to the C-2 selective azide opening of 2,3-epoxy alcohols are few, though isolated cases arising out of steric requirements[4] or the use of 2-trimethylsilyl-2,3-epoxy alcohols[10] have been reported. We have now developed a methodology to achieve the C-2 selective azide opening of *trans*-2,3-epoxy alcohols by the combination of NaN_3 and phenylboronic acid ($PhB(OH)_2$).

Although the C-2 selective azide opening reaction of 2,3-epoxy alcohols devoid of any steric and/or electronic bias has never been reported, we anticipated that the ring opening of such epoxy alcohols with NaN_3 and $PhB(OH)_2$ may occur regioselectively at the C-2 position by directing effect of $PhB(OH)_2$, as shown in Scheme 1. Indeed, this was realized in practice very efficiently by using 3 equiv. of NaN_3 and 2 equiv. of $PhB(OH)_2$ in hot DMF to provide phenylboronates of the corresponding 2-azido-1,3-diols in high yields.



Scheme 1

PII: S0040-4039(99)00798-4

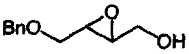
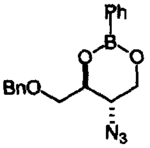
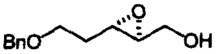
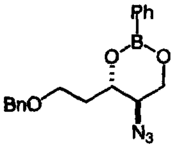
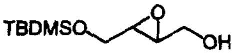
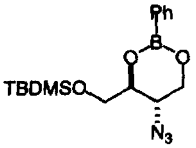
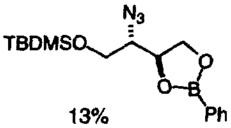
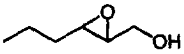
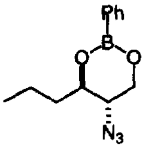
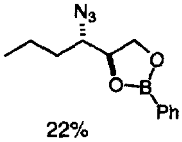
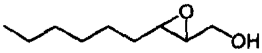
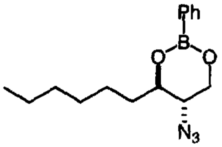
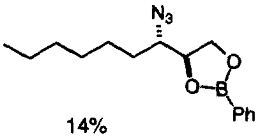
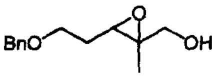
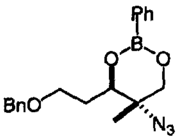
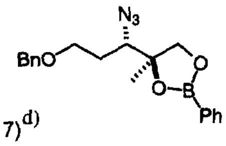
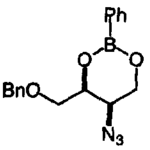
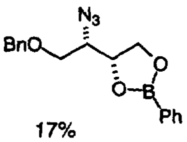
The representative results are summarized in Table 1. As shown, the ring-opening reactions of *trans*-4-benzyloxy- and *trans*-5-benzyloxy-2,3-epoxy alcohols with NaN_3 and $PhB(OH)_2$ occurred exclusively at the C-2 position to give phenylboronates of *trans*-2-azido-1,3-diols as a single product in 99% and 94% yields, respectively (entries 1 and 2). Similarly, the reaction of an analogous substrate having a silyloxy group proceeded cleanly to afford the C-2 azido-compound predominantly (entry 3). Thus, all the reactions of disubstituted *trans*-2,3-epoxy alcohols with NaN_3 and $PhB(OH)_2$ provided the corresponding phenylboronates of *trans*-2-azido-1,3-diols exclusively or predominantly (entries 1-5). The stereochemistry of the derived products were confirmed unambigously by NMR analyses and sodium periodate oxidation of the corresponding diols.[11] It is noteworthy that the phenylboronates thus obtained were very stable and could be easily purified by silica gel column chromatography and stored in a refrigerator for a long time without any appreciable decomposition.[12]

In contrast to the reactions of *trans*-2,3-epoxy alcohols, the corresponding *cis*-analogs were found to react sluggishly to provide lower yields of products presumably due to steric hindrance, though the reaction furnished the C-2 azide as the major product (entry 7). The result in Table 1 also demonstrates that the substrates having an ether oxygen in the side chain react faster and with higher regioselectivity than those having no such functionality (entries 1 and 2 vs. entries 4 and 5), which can be accounted for the chelation effect. It is also evident that the regioselectivity was not observed in the reaction of a trisubstituted *trans*-2,3-epoxy alcohol (entry 6).

It is of interest to note that the present procedure is the first example in realizing the C-2 selective azide opening reaction of disubstituted *trans*-2,3-epoxy alcohols having no particular steric and electronic bias. It may be noted that the reactions of *trans*-4-benzyloxy-2,3-epoxy alcohol (the substrate in entry 1) with $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ in benzene (70 °C) and with NaN_3-NH_4Cl in aqueous 2-methoxyethanol (124 °C) have been studied by Sharpless et al. to give a 6:1 and 1:1 mixture of the corresponding C-3 and C-2 azido-isomers, respectively.[6] They have also observed that the reactions of *trans*-2,3-epoxy-1-hexanol (the substrate in entry 4) with $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ in benzene (70 °C) and with NaN_3-NH_4Cl in aqueous MeOH (65 °C) gave a 5.8:1 and 36:1 mixture of the corresponding C-3 and C-2 azides, respectively.[6] Thus, the former methods/reagents have been known to produce 3-azido-1,2-diols regioselectively or predominantly.

In conclusion, we have developed a highly C-2 selective azide opening reaction of *trans*-2,3-epoxy alcohols through a combination of NaN_3 and $PhB(OH)_2$. Since a wide variety of optically active 2,3-epoxy alcohols are readily available via the Katsuki-Sharpless asymmetric epoxidation,[13] the present method will provide a convenient and selective way to prepare the phenylboronates of *trans*-2-azido-1,3-diols, thereby making it very useful in organic synthesis.

Table 1. Reaction of 2,3-Epoxy Alcohols with NaN_3 and $PhB(OH)_2$ in DMF.[a]

Entry	Substrate	Time (h)	Product Isolated Yield
1		4.5	 99%
2	 [b]	18	 94%
3		7	 77% +  13%
4		27	 78% +  22%
5		48[c]	 81% +  14%
6		44	 +  86% (5 : 7)[d]
7		65	 36% +  17%

[a] The reaction was carried out using NaN_3 (3 equiv.) and $PhB(OH)_2$ (2 equiv.) in DMF at 70°C.

[b] A chiral substrate.

[c] The reaction was carried out using NaN_3 (2 equiv.) and $PhB(OH)_2$ (1.3 equiv.) in DMF at 70°C.

[d] An inseparable mixture.

Acknowledgment. We are grateful to the Ciba-Geigy Foundation (Japan) for the Promotion of Science for financial support. This work was also supported by a Grant-in-Aid for JSPS Fellows (No. 2709) and Grants-in-Aid for Scientific Research on Priority Areas (No. 706 : Dynamic Control of Stereochemistry and No. 08245101) from the Ministry of Education, Science, Sports and Culture of Japan.

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11 The stereochemistry of two phenylboronates in entry 7 was confirmed by identification with that of authentic samples which were synthesized by phenylboronation of the corresponding 2-azido-1,3-diol and 3-azido-1,2-diol, respectively, readily prepared according to ref. 6.

12 The boronates are hydrolyzed to the corresponding diols by treatment with pinacol or 1,3-propanediol in aqueous acetone.

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