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An Efficient Method For The Preparation of Optically Active 4-Hydroxy-Δ^2-Isoxazolines

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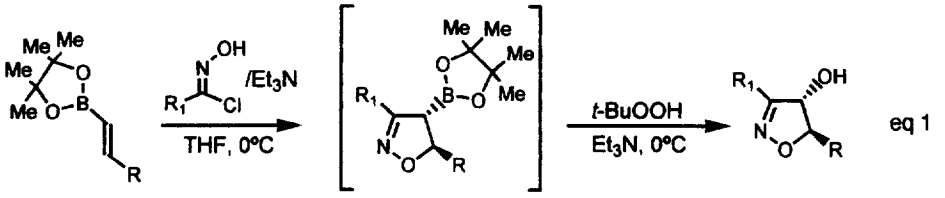
Abstract: In this letter we report a method for the preparation of optically active 4-hydroxy-Δ^2-isoxazolines. This methodology relies on the use of a camphorsultam substituted vinylboronic ester which upon nitrile oxide cycloaddition and oxidation affords the optically active 4-hydroxy-Δ^2-isoxazolines in good yield. © 1997 Elsevier Science Ltd.

We have shown previously that vinylboronic esters are useful precursors for the preparation of 4-hydroxy-5-substituted-Δ^2-isoxazolines.[1] This conversion is carried out by employing a nitrile oxide cycloaddition/oxidation sequence with 1,2-disubstituted vinylboronic esters. The nitrile oxide cycloaddition occurs with excellent regioselectivity to afford the 4-boronic ester substituted cycloadduct which is not isolated but is directly oxidized to afford the hydroxy Δ^2-isoxazolines (eq 1).[1] In this letter we wish to report on the extension of this methodology to the preparation of optically active 4-hydroxy-5-substituted-Δ^2-isoxazolines.



eq 1

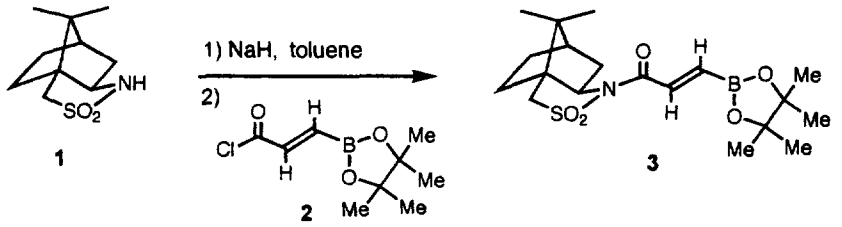
Jäger and others have shown 4-hydroxy-Δ^2-isoxazolines to be versatile intermediates for the synthesis of amino sugars and a number of other biologically important molecules.[2] Although a variety of methods have been reported for the preparation of racemic 4-hydroxy-Δ^2-isoxazolines[3] a very limited number of procedures are available for the preparation of optically active 4-hydroxy-Δ^2-isoxazolines.[4]

There are potentially two ways in which our original methodology could be modified to afford optically active 4-hydroxy-5-substituted-Δ^2-isoxazolines. The first of these would be to employ an optically active diol in place of pinacol on the vinylboronic ester. We have explored this possibility and the results of these studies will be reported separately. The other possible route would be to install a chiral auxiliary on the other end of

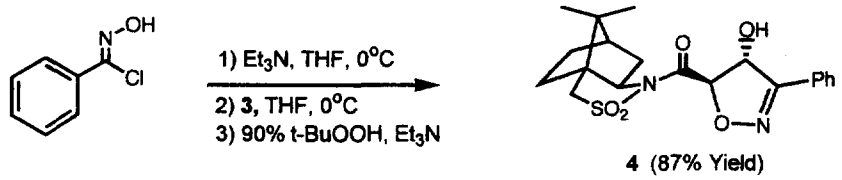
Dedicated to the memory of Professor Wolfgang Oppolzer

the vinylboronic ester, carry out the cycloaddition/oxidation, and obtain the product as a mixture of diastereomeric 4-hydroxy-5-substituted-Δ^2-isoxazolines. In light of the previous studies of Curran[5] and others the second route seemed more attractive.

Curran and Heffner[6] have shown Oppolzer's camphorsultam (**1**) to be an excellent chiral auxiliary for nitrile oxide cycloadditions; however, when a crotonyl substituted sultam was employed the diastereoselectivity was high (~9:1), although the regioselectivity was low.[6] In our earlier studies we have shown the boronic ester to be an excellent group for directing the regioselectivity in 1,2-disubstituted vinylboronic ester cycloadditions with nitrile oxides.[1] After considering all of the above information it appeared that the Oppolzer's camphorsultam substituted vinylboronic ester **3** might prove to be useful for the preparation of optically active 4-hydroxy-5-substituted-Δ^2-isoxazolines. Vaultier and coworkers[7] have previously described the preparation of the boronic ester substituted acid chloride (**2**).[7] Reaction of **2** with Oppolzer's sultam (**1**) afforded the desired optically active vinylboronic ester (**3**).



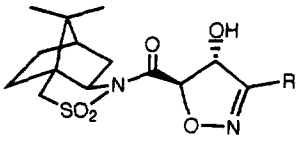
We were delighted to find that reaction of the camphorsultam substituted vinylboronic ester (**3**) with benzonitrile oxide under conditions employed previously for achiral vinylboronic esters[1] resulted in an 87% isolated yield of the camphorsultam substituted 4-hydroxy-Δ^2-isoxazoline (**4**). None of the other diastereomer or regioisomer could be detected in the ^{1}H NMR spectra of the crude reaction mixture. These results encouraged us to further explore this route for the preparation of optically active 4-hydroxy-5-substituted-Δ^2-isoxazolines.



4 (87% Yield)

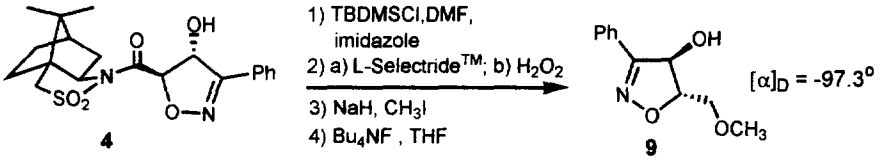
The procedure employed in these reactions involves reaction of the nitrile oxide with vinylboronic ester **3**. Upon completion of the cycloaddition (TLC), *t*-BuOOH (*CAUTION!*) and Et_3N are added.[1] Some of the

optically active 4-hydroxy-5-substituted-Δ^2-isoxazolines, (and their isolated yields), prepared via this route are shown below. It is important to note that although the reaction afforded good isolated yields of optically active 3-aryl- and 3-alkyl-4-hydroxy-Δ^2-isoxazolines, (**5-8**), the yields with other nitrile oxides was low. A modification in the above procedure was found to provide a solution to this problem. The preparation of optically active 4-hydroxy-5-substituted-Δ^2-isoxazolines with electron withdrawing groups in the 3-position will be reported separately.



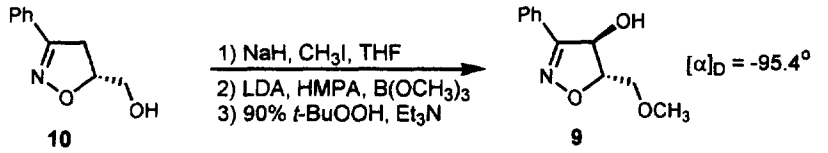
5; R=*p*-MeOC$_6$H$_4$ (93%)
6; R=*p*-BrC$_6$H$_4$ (84%)
7; R=*t*-Butyl (67%)
8; R=CH$_3$ (70%)

One of the major questions which had to be answered about the cycloadducts obtained from these reactions was that of absolute stereochemistry. The *trans* relationship between the C4-hydroxyl group and the C5-amide could be established from the coupling constant of the protons on C4 and C5.[8] The absolute stereochemistry shown is that which would be predicted if vinylboronic ester **3** reacted with nitrile oxides with the same facial selectivity displayed by other camphorsultam substituted α,β-unsaturated amides. [5] Confirmation of the absolute stereochemistry of cycloadduct **4** was obtained by conversion into **9** by the route shown below.



4 **9**

Isoxazoline **10**[5] of known absolute stereochemistry, previously prepared by Curran, was carried through the sequence of steps shown below to afford isoxazoline **9**, which had spectral properties identical to **9** derived from the cycloaddition/oxidation route employing **3**.



10 **9**

In these cycloadditions it is important to note the high degree of regioselectivity displayed by the vinylboronic ester in nitrile oxide cycloadditions. Further investigations into this high regioselectivity are

currently underway. We have previously reported that vinylboronic esters are very reactive dipolarophiles in 1,3-dipolar cycloadditions with nitrile oxides.[9] This high reactivity undoubtedly plays a role in the high yields and selectivity obtained in this method for preparation of optically active 4-hydroxy-5-substituted-Δ^2-isoxazolines. Further studies, including the employment of the amino-diols produced by LAH reduction of the optically active hydroxy isoxazolines in the synthesis of natural products, are currently underway.[10]

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10. All yields shown are isolated yields, and all new compounds gave satisfactory spectroscopic data, (^{1}H NMR, ^{13}C NMR, IR, and HRMS).

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