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Asymmetric synthesis of anti-1,2-amino alcohols via the Borono-Mannich reaction: a formal synthesis of (-)-swainsonine

Christopher W. G. Au
University of Wollongong, cwga289@uow.edu.au

Stephen G. Pyne
University of Wollongong, spyne@uow.edu.au

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Abstract

Chiral α-hydroxy-aldehydes generated in situ by the ADH reaction of vinyl sulfones undergo a borono-Mannich reaction with β-styrenyl boronic acid and primary amines to give *anti*-1,2-amino alcohols in high enantiomeric purities (ee 83-95%). This new method allows much more rapid access to these valuable chiral building blocks that has been used in a short formal synthesis (10 synthetic steps from 4-penten-1-ol) of (-)-swainsonine.

Keywords

Asymmetric, synthesis, anti, amino, alcohols, via, Borono, Mannich, reaction, formal, synthesis, swainsonine, CMMB

Disciplines

Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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Asymmetric Synthesis of *Anti*-1,2-Amino Alcohols via the Borono-Mannich Reaction: A Formal Synthesis of (-)-Swainsonine

Christopher W. G. Au and Stephen G. Pyne*

Department of Chemistry, University of Wollongong, Wollongong, New South Wales, 2522, Australia

spyne@uow.edu.au

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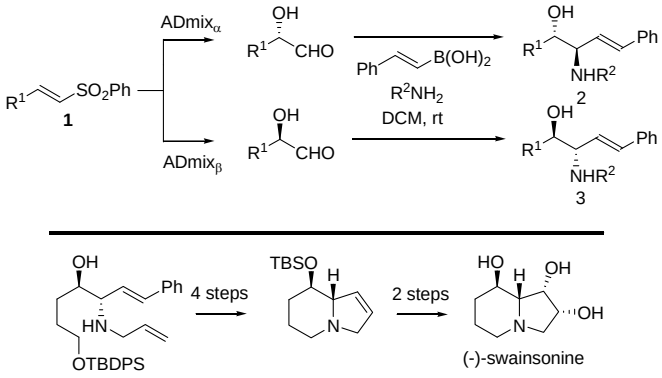
ABSTRACT

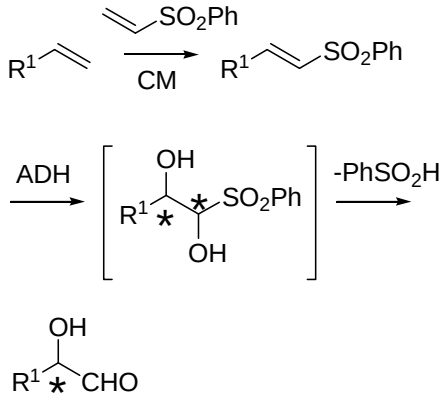


Abstract: Chiral α–hydroxy-aldehydes generated in situ by the ADH reaction of vinyl sulfones undergo a borono-Mannich reaction with β-styrenyl boronic acid and primary amines to give *anti*-1,2-amino alcohols in high enantiomeric purities (ee 83-95%). This new method allows much more rapid access to these valuable chiral building blocks that has been used in a short formal synthesis (10 synthetic steps from 4-penten-1-ol) of (-)-swainsonine.

In 1998, Petasis reported the synthesis of *anti*-1,2-amino alcohols from a borono-Mannich reaction of aryl or vinyl boronic acids, with primary or secondary amines and chiral α–hydroxy-aldehydes.[1] The latter were derived from carbohydrates which limited the generality of this reaction as enantiomerically enriched chiral α–hydroxy-aldehydes were not generally available. A more recent paper by Evans,[2] however, showed that these valuable substrates could be prepared *in situ* from the Sharpless asymmetric dihydroxylation (ADH) reaction of vinyl sulfones (Scheme 1). We report here that chiral α–hydroxy-aldehydes generated in situ by this method

undergo the borono-Mannich reaction with β-styrenyl boronic acid and primary amines to give *anti*-1,2-amino alcohols in high enantiomeric purities. This new method allows much more rapid access to these valuable chiral building blocks. More specifically, the derived *anti*-1,2-amino alcohol diene products, obtained using allylamine, are valuable precursors for alkaloid synthesis,[3] as further demonstrated here by a short, formal synthesis of the important natural product (-)-swainsonine. [4]

Scheme 1



Results and Discussion

The (*E*)-vinyl sulfones **1a,b** were readily prepared from their corresponding terminal alkenes via either cross metathesis with phenyl vinyl sulfone ((*E*) : (*Z*) = >99 : <1),[5] (Scheme 1) or by iodosulfonation followed by elimination of HI ((*E*) : (*Z*) = 98 : 2, see Supporting Information).[6]

Treatment of vinyl sulfone **1a** with either ADmix$_\alpha$ or ADmix$_\beta$, under the conditions described by Evans,[2] gave, after extraction into EtOAc and evaporation, material that showed no characteristic, downfield aldehyde ^{1}H NMR resonances, more consistent with a mixture of acetal-like structures. This material was then treated with β-styrenyl boronic acid (1.00 mol equiv. relative to **1a**) and allylamine (1.06 mol equiv. relative to **1a**) in CH_2Cl_2 at rt for 40 h to give the *anti*-1,2-amino alcohol dienes **2a** (R^2 = allyl) and **3a** (R^2 = allyl), respectively (Scheme 2, Table 1, entries 1 and 2). These compounds were isolated as single diastereomers in 44 and 51% overall yields for the two step sequence, respectively, from **1a**. The isomeric *syn*-1,2-amino alcohol dienes could not be detected. The enantiomeric purities of these products was high, 91% and 94%, respectively, as determined by ^{19}F NMR spectroscopic analysis of their corresponding Mosher esters (see Supporting Information). When these reactions were repeated using 4-methoxybenzylamine ($PMBNH_2$), the *anti*-1,2-amino alcohol dienes **2a** (R^2 = PMB) and **3a** (R^2 = PMB), were isolated as single diastereomers in 46 and 43% overall yields and had enantiomeric purities of 91% and 95%, respectively (Scheme 2, Table 1, entries 3 and 4).

When this sequence of reactions was performed starting with vinyl sulfone **1a** and using the secondary amine, morpholine and the aromatic amine, 4-methoxyaniline ($PMPNH_2$), the overall yields were disappointing. The morpholine derived *anti*-1,2-amino alcohol product was obtained as a single diastereomer in only 12% yield (ee not determined), while none of the adduct **2a** (R^2 = PMP) could be isolated.

Scheme 2

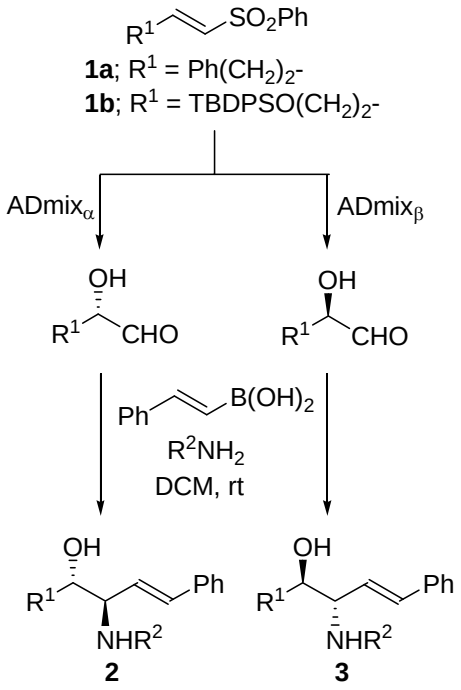


Table 1. Synthesis of **2** and **3** (Scheme 2).

Entry	Vinyl sulfone	AD mix	Amine R^2	Overall yield (%) from **1**[a]	Ee (%)[b]
1	**1a**	α	allyl	44	91
2	**1a**	β	allyl	51	94
3	**1a**	α	PMB	46	91
4	**1a**	β	PMB	43	95
5	**1b**	α	allyl	35	83
6	**1b**	β	allyl	38	93

[a]Yield of **2** or **3** after purification by column chromatography. [b]Determined by ^{19}F NMR spectroscopy on the corresponding Mosher ester.

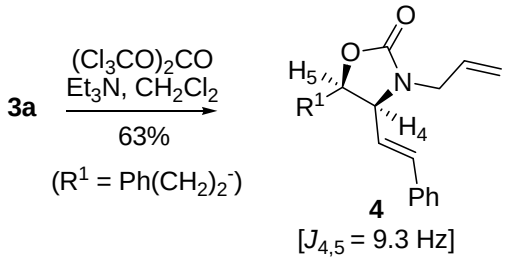
Treatment of the TBDPS protected vinyl sulfone **1b** with either ADmix$_\alpha$ or ADmix$_\beta$, followed by treatment of the crude oxidation product with β-styrenyl boronic acid and allylamine gave the *anti*-1,2-amino alcohol dienes **2b** (R^2 = allyl) and **3b** (R^2 = allyl), respectively (Scheme 2, Table 1, entries 5 and 6) in overall yields of 35 and 38%, respectively, for the two step sequence. The enantiomeric purities of these products however was

significantly different, with ee's determined as 83% and 93%, respectively.

While in general the overall yields of **2** and **3** were only modest, the overall brevity of their synthesis (total of 3 steps) compares more than favourably with previously published methods for these *anti*-1,2-amino alcohol dienes (R^2 = allyl) that involve the ring opening of vinyl epoxides with allylamine, where the former substrates requires six synthetic steps from commercially available starting materials.[3a,7,8] Furthermore, these yields are based on 1.0 equiv of **1** and 1.0 equiv of β-styrenyl boronic acid.[9] These modest yields most likely reflect the instability of the α–hydroxy-aldehyde or their acetal-like intermediates, however the high ee's of the product 1,2-amino alcohols indicates that racemization of these intermediates is not a major problem.

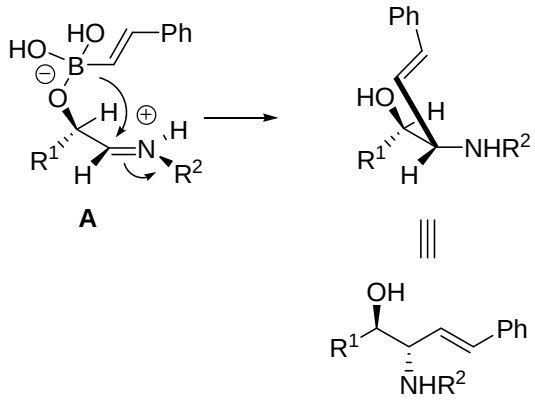
To verify the relative stereochemistry of **3a** (R^2 = allyl) it was converted to the oxazolidinone **4** (Scheme 3) by treatment with triphosgene under basic conditions. The 9.3 Hz vicinal coupling constant, $J_{4,5}$, in the ^{1}H NMR spectrum of **4** was consistent with the 4,5-*cis* relative stereochemistry.[3g, 7]

Scheme 3



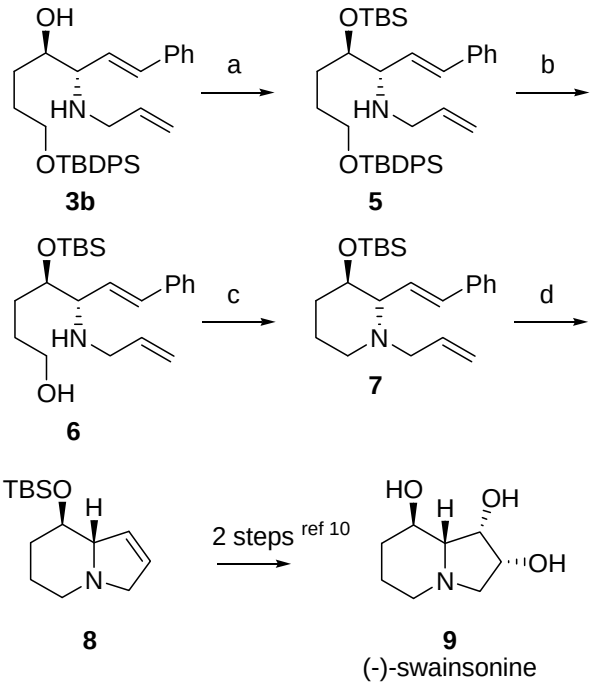
While the exact mechanism of the borono-Mannich reaction is not known, we speculate that these reactions occur via the boronate complex intermediate **A** (Scheme 4) in which the iminium ion adopts the reactive conformation shown to minimize 1,3-allylic strain.

Scheme 4



To demonstrate the utility of these substrates further, the *anti*-1,2-amino alcohol diene **3b** (R^2 = allyl) was converted in four steps to the known indolizidine **8**[10,11] as shown in Scheme 5. Protection of the secondary hydroxyl of **3b** (R^2 = allyl) as its TBS ether and then deprotection of the primary TBDPS ether under basic conditions[11] gave the amino alcohol **6**. Cyclization of this compound by intramolecular *N*-alkylation (Ph_3P, CBr_4, Et_3N)[3g,13] gave the piperidine derivative **7** in 71% yield (Scheme 3). The ring-closing metathesis of **7**, employing Ti(O*i*-Pr)$_4$ as a Lewis acid to protect the amino group *in situ* by complexation,[14] provided the silica gel sensitive indolizidine **8** ($[\alpha]^{26}_D$ -72, c 0.65, benzene) in 80% yield after purification on basic alumina. This compound has been prepared previously, in >99% ee ($[\alpha]^{20}_D$ -91.73, *c* 0.955, benzene)[10,15] and in racemic form and converted to (-)[9] and (±)-swainsonine,[12] respectively. Thus our synthesis of **8** represents a formal asymmetric synthesis of (-)-swainsonine **9** in 10 steps from commercially available 4-penten-1-ol. This number of steps compares more than favourably with earlier syntheses of **9** that typically involve 10 or more steps.[4]

Scheme 5



Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2.5 h, 70%. (b) KOH, MeOH, reflux, 7 h, 60%. (c) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, 0 °C, 2 h, 71%. (d) Ti(O*i*-Pr)$_4$, Grubbs' II cat., CH_2Cl_2, reflux, 2.5 h, 80%.

In conclusion, chiral α–hydroxy-aldehydes generated in situ by the ADH reaction of vinyl sulfones undergo the borono-Mannich reaction with β-styrenyl boronic acid and primary amines to give *anti*-1,2-amino alcohols in high enantiomeric purities (83-95%). This new method allows a much more rapid access to these valuable chiral building blocks that have been used in a formal synthesis of (-)-swainsonine in 10 synthetic steps.

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Supporting Information Available Full experimental details and characterization data for all compounds. Copies of the ^{1}H and ^{13}C NMR spectra of **1a,b**, **2a,b**, **3a,b**, **4-8** and copies of the ^{1}H and ^{19}F NMR spectra of the Mosher esters of **2a,b** and **3a,b** in $CDCl_3$ solution.

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