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Diastereoselective Synthesis of 1,4-Amino Alcohols *via* 1,4-Stereochemical Control using Sulfoximines

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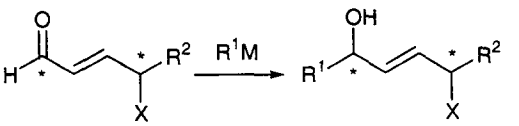
Abstract: A diastereoselective synthesis of 1,4-amino alcohols can be achieved from a highly diastereoselective reduction of a γ-keto-vinyl sulfoximine followed by C-methylation and then a highly diastereoselective palladium(0) catalysed allylic sulfoximine to allylic sulfinamide rearrangement with 1,4-stereochemical control from a remote hydroxyl group.

Key words: asymmetric induction, catalysis, diastereoselection, palladium, sulfoximines, reduction

Optically active substrates of the general type **2**, which have two stereogenic centres in a 1,4-stereochemical relationship that are separated by a carbon-carbon double bond, are attractive potential building blocks for preparing optically active natural products and novel bioactive molecules. 1,4-Diols and 1,4-amino alcohols of the type **2** (X= OH or NHR) have been prepared with modest to good 1,4-asymmetric induction from the addition of organometallic reagents to *O*-protected γ-hydroxy enals **1** (X = OMOM)[1] and *N*-protected γ-amino enals **1** (X = NBn_2)[2] respectively (eq 1).



1 **2** (eq. 1)

Compounds **1** (X = OMOM) and **1** (X = NBn_2) were prepared from the Wittig-Horner reaction of *O*-protected α-hydroxy aldehydes and *N*-protected α-amino aldehydes, respectively. The former aldehydes are not directly available in enantiomerically pure form while the latter aldehydes are available in a few synthetic steps from naturally occurring α-amino acids.[3] This methodology therefore, is not of general utility nor is it particularly diastereoselective, and it is clearly only convenient for the preparation of 1,4-amino alcohols of the type **2** from naturally occurring α-amino acids. Knochel has disclosed a method for improving the diastereoselectivity (d.r. = 94-96:6-4) on compounds of the type **1** (X= OTBDPS) by using organozinc reagents and a chiral titanium catalyst.[4] More recently Otera[5] has reported a complementary approach to 1,4-

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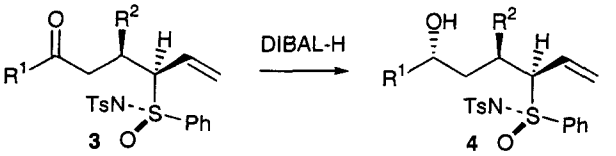
diols of the type **2** (X = OH) by the reduction of *O*-protected γ-hydroxyketones with L-selectride. The diastereoselectivities of these reductions, however, were modest (dr = 75-70:25-30). The *O*-acetates of compounds of the type **2** (X = Cl, $R^1 = R^2$) have been prepared in high diastereomeric purity, but in racemic form, from the palladium-catalysed chloroacetoxylation of symmetric 1,4-disubstituted butadienes.[6]

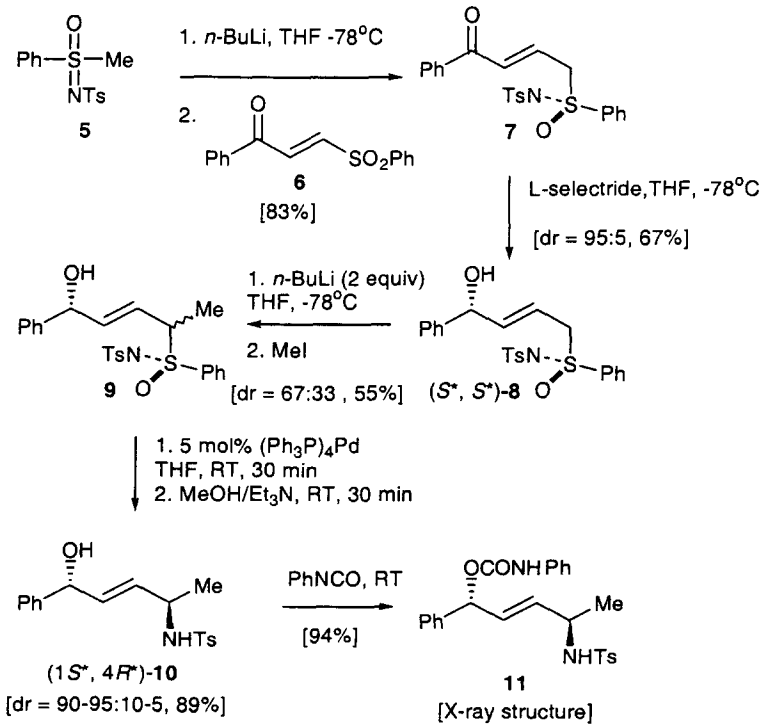
In related studies on remote asymmetric induction we have found that γ-sulfonimidoyl ketones **3** undergo highly diastereoselective reductions with DIBAL-H.[7] The high level of diastereoselectivity was attributed to the *N*-Ts group on the sulfoximine moiety that effectively sterically shields one face of the carbonyl group from attack by hydride (eq 2). We now report that compounds of the type **2** (X = NHTs) can be prepared with high diastereochemical control *via* two tandem 1,4-diastereoselective reactions involving the allylic sulfoximine group.



(eq. 2)

Addition of a THF solution of the β-sulfonyl-enone **6**[8] to a THF solution of lithiated racemic *N*-tosyl-*S*-methyl-*S*-phenylsulfoximine **5** at –78°C followed by warming to 0°C for 40 min gave compound **7** in 83 % yield after purification by column chromatography.[7]

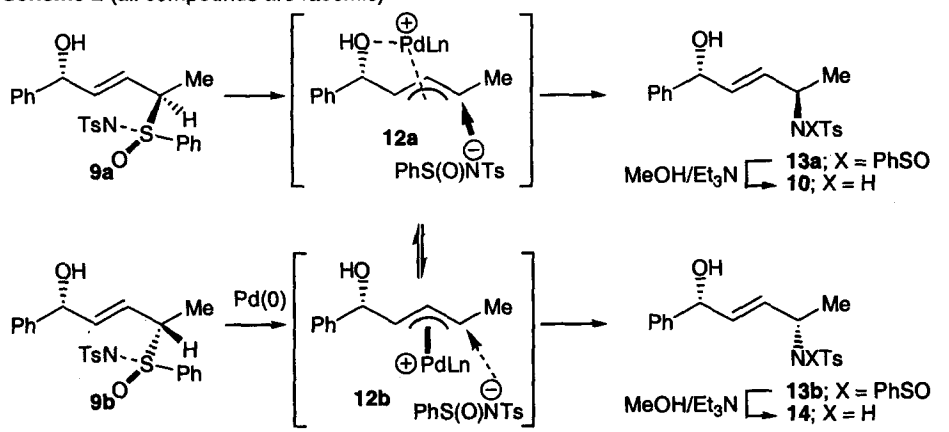
Scheme 1 (all compounds are racemic)



Reduction of **7** with L-selectride (2 mol. equiv.) in THF at –78°C for 2h, followed by a basic hydrogen peroxide work up, gave the alcohol **8** with high diastereoselectivity (dr >95:< 5, from ^{1}H NMR analysis at 400 MHz). Diastereomerically pure **8** was obtained in 67% yield after purification of the crude reaction mixture on silica gel. Interestingly, DIBAL-H gave **8** as a 50:50 mixture of diastereomers. The relative stereochemistry of **8** could not be determined since suitable crystals for X-ray analysis could not be obtained. However, based on our previous experience with the chemistry highlighted in equation 2 we expected that **8** has the (*S**, *S**)-relative stereochemistry.

Treatment of a THF solution of diastereomerically pure **8** at –78°C with 2.2 mol. equivalents of *n*-butyllithium for 30 min followed by the addition of iodomethane (1.2 mol. equiv., -78°C for 3h) gave the C-methylated derivative **9** as a 67:33 mixture of diastereomers in 55% yield. The major diastereomer could be isolated pure by careful column chromatography. Treatment of the 67:33 diastereomeric mixture of **9** with 5 mol% tetrakis(triphenylphosphine)palladium(0) in THF at room temperature for 30 min[9] followed by removal of the THF *in vacuo* and then the addition of methanol/triethylamine,[10] to convert the product allylic sulfinamide to its corresponding sulfonamide, gave **10** in 89% yield as a 90:10 mixture of diastereomers (from ^{1}H NMR analysis at 400 MHz). Under identical conditions the major diastereomer of **9** gave **10** as essentially a single diastereomer (dr = 95:5). The relative *anti*-stereochemistry of **10** was established from a single crystal X-ray structure determination on its carbamate derivative **11**.[11] Thus both diastereomeric allylic sulfoximines of **9** (**9a** and **9b**) give predominantly the same diastereomeric allylic sulfinamide rearrangement product **13a** and minor amounts of **13b** (Scheme 2).[12]

Scheme 2 (all compounds are racemic)



The diastereomers **9a** and **9b** would be expected to give the diastereomeric *syn*-η^3-palladium-allyl cation complexes **12a** and **12b**, respectively, that would be expected to give the diastereomeric allylic sulfinamides **13a** and **13b** respectively, upon nucleophilic attack of the ambident sulfinamide anion through its nitrogen atom.[7,13] Complex **12a**, however, would be predicted to be thermodynamically more favoured than **12b** due to coordination of the palladium to the hydroxyl group. While such coordination in **12b** is possible this

intermediate would suffer from 1,3-allylic strain between the Ph substituent and the central hydrogen atom of the allyl cation moiety. Thus the high diastereoselectivity of these palladium(0) catalysed reactions suggests that the thermodynamically less stable complex **12b** rapidly interconverts to the thermodynamically more stable complex **12a** and that this interconversion is more rapid than nucleophilic attack by sulfinamide anion on these complexes. It is also possible that these palladium(0) catalysed reactions are under thermodynamic control (through the interconversion of **13a** and **13b** *via* **12a** and **12b**) and experiments are under way to investigate the mechanistic details of these reactions. While we have only examined the palladium(0) chemistry of racemic allylic sulfoximines, their optically active versions[9] would be expected to give optically active **11** and, in the presence of external nucleophiles,[10] optically active compounds of the general structure **2**. In conclusion, we have found that high levels of 1,4-stereochemical control can be achieved in both the reduction of a γ-keto vinyl sulfoximine and in the palladium(0) catalysed reactions of an allylic sulfoximine from a remote hydroxyl group. The hydroxyl group should also be a useful moiety for remote stereochemical control in other palladium catalysed allylation reactions of acyclic systems. Indeed, recent reports by de Meijere[14] and Cook[15] have shown high levels of 1,2-asymmetric induction can be achieved in allylic substrates having an adjacent stereocentre.

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11. Details will be published in a full paper.
12. If **9a** gives 95% **13a** and 5% **13b** in the reaction of **9** as a 67:33 mixture of diastereoisomers then 80% of **9b** must give **13a**.
13. The sulfinamide group is also chiral and thus **13a,b** could each have 2 diastereomeric forms. In this discussion the chirality of the sulfinamide group has been ignored. Experiments are in progress to investigate this influence of this stereocentre on the product diastereoselectivity
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